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EDUCATIONALLY INTERVENING THE USE OF POTENTIALLY HARMFUL MEDICATION AMONG RESIDENTS IN INSTITUTIONAL SETTINGS

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Academic dissertation

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To Vesa with love

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Abbreviations

A	= Anxiolytic
ACTRN	= Australian New Zealand Clinical Trials Registry
AD	= Alzheimer's Disease
ADL	= Activities of Daily Living
ALF	= Assisted Living Facility
AT	= Atypical Antipsychotic
ATC	= Anatomic Therapeutic Chemical classification
CDR	= Clinical Dementia Rating
CI	= Confidence Interval
CN	= Conventional Neuroleptic
CNS	= Central Nervous System
DAP	= Drug with Anticholinergic Properties
DBI	= Drug Burden Index
DDI	= Drug-Drug Interaction
EP	= Extrapyramidal
GEE	= Generalized Estimating Equation
H	= Hypnotic
HR	= Hazard Ratio
HRQoL	= Health Related Quality of Life
IRR	= Incidence Rate Ratio
LTCF	= Long-Term Care Facility
LTCW	= Long-Term Care Ward
MAI	= Medication Appropriateness Index
MMSE	= Mini-Mental State Examination
MNA	= Mini-Nutritional Assessment
NH	= Nursing Home
NHD	= Nursing Home for people with Dementia
NNH	= Number Needed to Harm
NSAID	= Non-Steroidal Anti-Inflammatory Drug
OR	= Odds Ratio
PHM	= Potentially Harmful Medication
PID	= Potentially Inappropriate Drug
PIM	= Potentially Inappropriate Medication
PPI	= Proton Pump Inhibitor
PWB	= Psychological Well-Being
QoL	= Quality of life
RAI	= Resident Assessment Instrument
RCT	= Randomized Controlled Trial
RR	= Relative Risk
S	= Sedative
SAA	= Serum Anticholinergic Activity
SD	=Standard Deviation
SSRI	= Selective Serotonin Reuptake Inhibitor
TCA	= Tricyclic Antidepressant
WHO	= World Health Organization
15D	= 15-Dimensional
95% CI	= 95% Confidence Interval

Definitions

Potentially harmful medication (PHM)	PHMs in this study: 1. Beers' 2003 Potentially inappropriate drugs (PIDs), 2. Drugs with anticholinergic properties (DAPS) according to Rudolph's anticholinergic risk scale (ARS), Beers' 2003 anticholinergic drugs, and the Svenska Socialstyrelsen 2010 list, 3. Use of >2 psychotropics concomitantly according to Svenska Socialstyrelsen, 4. Proton Pump Inhibitors (PPIs), 5. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
Potentially inappropriate drug (PID)	PID is a term first used in Beers' 1997 updated criteria. PIDs are drugs that should be avoided among people aged ≥65 years.
Potentially inappropriate medication (PIM)	PIM refers to inappropriate drugs according to various international criteria.
Older people	People aged ≥65 years.
Educational intervention	An educational intervention seeks to reform an older practice through training. In this study, education is based on constructive learning theory. This means learning with an active process in which learners construct new concepts based upon their previous knowledge to solve problems.
Nursing home	Institutional settings providing 24-hour care for older people with multimorbidity and need for assistance in activities of daily living (ADL) and instrumental activities of daily living (IADL).
Assisted living facility	Home-like environment that provides room and board for older people. Level of assistance and costs depend on each resident's needs according to medical conditions and ADL and IADL skills. Care available around the clock. Nowadays in Finland, an assisted living facility resident's need for assistance and the level of care are quite similar to those in nursing homes. Defined as an institutional setting in this study.

List of original publications

This thesis is based on the following original publications:

1. Juola AL, Pylkkanen S, Kautiainen H, Bell JS, Bjorkman MP, Finne-Soveri H, Soini H, Pitkälä KH. Burden of potentially harmful medications and the association with quality of life and mortality among institutionalized older people. J Am Med Dir Assoc 2016;17:276.e9-14.

2. Juola AL, Bjorkman MP, Pylkkanen S, Finne-Soveri H, Soini H, Kautiainen H, Bell JS, Pitkala K. Feasibility and baseline findings of an educational intervention in a randomized trial to optimize drug treatment among residents in assisted living facilities. Eur Geriatr Med 2014;5:195-9.

3. Pitkälä KH, Juola AL, Kautiainen H, Soini H, Finne-Soveri UH, Bell JS, Björkman M. Education to reduce potentially harmful medication use among residents of assisted living facilities: a randomized controlled trial. J Am Med Dir Assoc 2014;15:892-8.

4. Juola AL, Bjorkman MP, Pylkkanen S, Finne-Soveri H, Soini H, Kautiainen H, Bell JS, Pitkala KH. Nurse education to reduce harmful medication use in assisted living facilities: effects of a randomized controlled trial on falls and cognition. Drugs Aging 2015;32:947-55.

Abstract

Background: Institutionalized older people are frail and they suffer from a high number of comorbidities. Polypharmacy is also common. In older age, changes in pharmacokinetics often lead to slower metabolism and higher drug concentrations. Thus, older people are prone to adverse effects of drugs and their drug treatment is challenging.

Over the last few decades, several criteria have been developed to define potentially inappropriate medication for older people. Beers' list of inappropriate drugs in 1991 in USA was the first explicit criteria for inappropriate drugs, and it has been updated in 1997, 2003, 2012, and 2015. Many countries have developed their own criteria. There are also some implicit criteria for beneficial medication such as STOPP and START criteria.

Drugs with anticholinergic properties (DAPs) are known to be potentially harmful. Their use may lead to many adverse effects such as cognitive decline, delirium, falls, dry mouth, urinary retention, and constipation. Several criteria measure anticholinergic burden. However, no consensus exists regarding the best criteria for the adverse events related to the use of DAPs.

The use of psychotropic drugs among institutionalized older people has been excessive for many decades. US legislation has given instructions to reduce the use of psychotropic drugs in nursing homes since 1987. Psychotropic drugs may lead to a number of adverse effects such as cognitive decline, extrapyramidal symptoms, falls, and disabilities. The use of antipsychotics among older people with dementia is associated with strokes and increased risk for mortality. Although the adverse effects of antipsychotics are known, antipsychotic use in Finland remains high.

Nowadays there is also evidence that some commonly used medications, such as proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs), may not be safe in older people. The use of PPIs is associated with, for instance, *Clostridium difficile* infections and pneumonia and the use of NSAIDs with gastric and duodenal ulcer bleeding and heart failure.

There is a paucity of studies exploring how potentially harmful medications (PHMs) according to various criteria accumulate among institutionalized older people and how they affect their welfare and survival. Several randomized controlled trials (RCTs) have been performed to reduce the use of harmful drugs. Most of these trials have focused on psychotropics. Interventions have diminished the use of psychotropics. However, the effects on rate of falls, quality of life, and mortality remain unclear.

Aims: This study explored the use of PHMs among older people living in assisted living facilities in Helsinki and in nursing homes in Kouvola. PHMs were defined according to the literature. In a cluster RCT, the aim was to investigate the effect of staff training on the use of PHMs among residents in assisted living facilities in Helsinki and its outcomes. Specific aims were to clarify the use of PHMs (Studies 1 and 2), the burden and overlapping of PHMs, and their associations with residents' health-related quality of life (HRQoL), psychological well-being (PWB), and 3-year mortality (Study 1). Other aims were to evaluate the feasibility of educational intervention (Study 2) and the effect of the intervention on the use of PHMs and HRQoL, use of hospital days, and mortality among older people in assisted living facilities during a 12-month follow-up (Study 3), as well to evaluate the effect of educational intervention on residents' falls and cognition during a 12-month follow-up (Study 4).

Methods: Participants were recruited from assisted living facilities in Helsinki (Studies 1-4) and from nursing homes in Kouvola (Study 1). Participants or their closest proxy (in case of participants' MMSE <20) gave written consent to participate. Inclusion criteria were age ≥65 years and living permanently in assisted living facility in Helsinki or in nursing home in Kouvola, native Finnish speaking, using at least one drug, having estimated lifetime ≥ 6 months, and voluntary participation. Study 1 was a cross-sectional study with a 3-year follow-up for mortality. Studies 2-4 were based on a cluster RCT. Units had to be randomized instead of participants to avoid contamination of the intervention. Units were chosen with the aid of Resident Assessment Instrument (RAI) assessment, which was used to select wards with as similar as possible patient profiles, or case-mix. Altogether, 227 residents were included and randomized into either the intervention group (n=118) or the control group (n=109). The intervention was an educational intervention to staff, based on constructive learning theory. Nursing staff of the intervention wards received two afternoon training sessions about medication for older persons, both potentially inappropriate and beneficial. Physicians were also welcome to training. The learning process was activating and used patient cases. Nursing staff of the control wards received the same training after a one-year follow-up. The primary outcome measures were the proportion of persons using PHMs (Beers' drugs, DAPs, or >2 psychotropics) and the change in the number of PHMs. Secondary outcome measures were change in HRQoL according to the 15D HRQoL and in cognition during the 12-month follow-up. In addition, the number of falls and fallers and the use of health care services during the follow-up were retrieved from medical records. Mortality up to 12 months was compared between intervention and control arms.

Results: The characteristics of participants were quite similar in the intervention, control, and Kouvola group. Participants' mean age ranged from 83 to 84 years and the majority (65-77%) of participants were woman. The mean number of regular drugs was over 7. Charlson comorbidity index (a method calculating the risk of comorbidity on death) was highest in the intervention group, 3.2, and lowest in the Kouvola group, 2.2. The proportion of all participants using any harmful drug was 78%. In Study 1, there was a stepwise association between the use of PHMs according to three definitions (Beers' drugs 2003, DAPs, and use of >2 psychotropics concomitantly) and HRQoL, PWB, and self-rated health; the more criteria fulfilled, the lower the HRQoL, PWB, and self-rated health. Burden of PHMs was not associated with mortality in the 3-year follow-up.

In RCT, as an effect of intervention, the prevalence of PHMs, especially psychotropics, decreased significantly in the intervention group (-11.7%, 95% confidence interval (CI) -20.5 to -2.9; p=0.009), whereas there was no significant change in the control group (+3.4%, 95% CI -3.7 to 10.6; p=0.34). HRQoL decreased significantly less in the intervention group (-0.038, 95% CI -0.054 to -0.022) than in the control group (-0.072, 95% CI -0.089 to -0.055; p=0.005). Residents in the intervention group used significantly less hospital days than those in the control group, 1.4/person/year (95% CI 1.2 to 1.6) versus 2.3/person/year (95% CI 2.1 to 2.7), incidence rate ratio (IRR) for intervention group was 0.60, 95% CI 0.49 to 0.75; p <0.001 (adjusted for age, sex and comorbidities). There was no difference in the use of ambulatory services. Residents in the intervention wards fell significantly less than in the control wards. The age-, sex-, and comorbidity-adjusted IRR for falls in the intervention wards was 0.72 (95% CI 0.59 to 0.88; p <0.001). When exploring falls according to subgroups, residents with MMSE scores >10 had the greatest benefit from the intervention. No difference emerged between the groups in changes of cognition according to verbal fluency or clock drawing test or in one-year mortality.

Conclusions: A high burden of PHMs according to different criteria was associated with a lower quality of life. Nursing staff education on medication for older persons was beneficial. The use of PHMs, especially psychotropic medications, the rate of falls, and the use of hospital days all decreased more in the intervention group than in the control group. The quality of life decreased less in the intervention group than in the control group. However, no effect was observed on cognition or mortality, nor was there a difference in 3-year mortality according to burden of PHMs. The intervention was quite light and can easily be applied to other similar units.

Tiivistelmä (Finnish Abstract)

Tausta: Laitoksissa asuvat ikääntyneet ovat hauraita ja monisairaita. Heillä on myös usein monilääkitystä. Ikääntyneillä tapahtuvat muutokset farmakokinetiikassa johtavat usein metabolian hidastumiseen ja lääkeainepitoisuuksien nousuun. Näin ollen iäkkäät ovat herkkiä lääkeaineiden haittavaikutuksille ja heidän lääkehoitonsa on haastavaa.

Vanhuksille potentiaalisesti haitallisten lääkeaineiden tunnistamiseksi on viime vuosikymmenien aikana kehitetty useita eri kriteeristöjä. Vuonna 1991 USA:ssa julkaistu Beersin lista sopimattomista lääkeaineista oli ensimmäinen poissulkeva kriteeristö iäkkäille sopimattomista lääkkeistä ja sitä on päivitetty vuosina 1997, 2003, 2012 ja 2015. Monet maat ovat luoneet omat kriteeristönsä. STOPP ja START kriteeristöön sisältyy myös implisiittinen osio hyödyllisistä lääkeaineista.

Myös antikolinergisesti vaikuttavien lääkkeiden tiedetään olevan potentiaalisesti haitallisia. Niiden käyttö voi aiheuttaa monia haittavaikutuksia kuten kognition alenemista, sekavuutta, kaatumisia, suun kuivumista, virtsaamisvaikeuksia ja ummetusta. Antikolinergista taakkaa voidaan mitata monilla eri kriteereillä. Kuitenkaan ei ole päästy yhteisymmärrykseen siitä, mikä menetelmistä on parhaiten yhteydessä antikolinergisten lääkeaineiden käyttöön liittyviin haittatapahtumiin.

Psyykenlääkkeitä on käytetty laitoksissa asuvilla vanhuksilla liikaa vuosikymmenien ajan. USA:ssa lainsäädännöllä ohjeistettiin vähentämään psyykenlääkkeiden käyttöä vanhainkodeissa jo vuonna 1987. Psyykenlääkkeiden käyttöön voi liittyä haittavaikutuksia kuten kognition laskua, ektrapyramidaalioireita, kaatumisia ja toiminnanvajauksia. Antipsykoottien käyttöön muistisairailla vanhuksilla liittyy aivohalvauksien ja lisääntyneen kuolleisuuden riski. Huolimatta siitä, että psyykenlääkkeiden aiheuttamat haittatapahtumat tunnetaan, niiden käyttö myös Suomessa on pysynyt runsaana.

Nyttemmin on myös näyttöä siitä, että jotkin varsin yleisesti käytetyt lääkkeet kuten protonipumpun estäjät ja tulehduskipulääkkeet eivät mahdollisesti ole vanhuksille turvallisia. Happosalpaajien käyttö on yhteydessä esimerkiksi *Clostridium difficile*-infektioihin ja keuhkokuumeseen, tulehduskipulääkkeiden käyttö maha- ja pohjukkaissuoliverenvuotoihin ja sydämen vajaatoimintaan.

On varsin niukasti tutkimuksia, joissa on selvitetty eri perusteiden mukaisesti haitallisiksi katsottujen lääkkeiden kertymistä laitoksissa asuville vanhuksille ja miten se vaikuttaa heidän hyvinvointiinsa ja eloonjäämiseensä. Monia satunnaistettuja, kontrolloituja tutkimuksia on tehty haitallisten lääkkeiden käytön vähentämiseksi. Monet näistä tutkimuksista ovat keskittyneet psyykenlääkkeisiin. Interventioilla psyykenlääkkeiden käyttöä on saatu vähennettyä. Vaikutukset kaatumisten määrään, elämänlaatuun ja kuolleisuuteen ovat kuitenkin jääneet epäselviksi.

Tutkimuksen tavoitteet: Tällä tutkimuksella selvitettiin iäkkäiden helsinkiläisten palvelutalojen ja kouvolalaisten vanhainkotien asukkaiden potentiaalisesti haitallisten lääkkeiden käyttöä. Haitallisiksi katsotut lääkeaineet määriteltiin kirjallisuuden perusteella. Tutkimuksen tavoitteena oli ryhmäsatunnaistetussa, kontrolloidussa tutkimuksessa selvittää, oliko henkilökunnan koulutuksella vaikutusta helsinkiläisten palvelutalojen asukkaiden haitallisten lääkkeiden käyttöön ja sen seurauksiin. Erityistavoitteena oli selvittää potentiaalisesti haitallisten lääkkeiden käyttöä (osatyöt 1 ja 2), niiden taakkaa ja päällekkäisyyttä sekä yhteyttä asukkaiden terveyteen liittyvään elämänlaatuun, psyykkiseen hyvinvointiin ja kolmen vuoden kuolleisuuteen (osatyö 1). Muina tavoitteina oli myös selvittää koulutusintervention toteutettavuus (osatyö 2) ja intervention vaikutus palvelutalojen asukkaiden potentiaalisesti haitallisten lääkkeiden käyttöön, terveyteen liittyvään elämänlaatuun, sairaalapäivien käyttöön sekä kuolleisuuteen 12 kuukautta kestävänä seuranta-aikana (osatyö 3), sekä intervention vaikutus asukkaiden kaatumisiin ja kognitioon 12 kuukautta kestävänä seuranta-aikana (osatyö 4).

Menetelmät: Osallistujat rekrytoitiin helsinkiläisistä tehostetun palveluasumisen yksiköistä (osatyöt 1-4) ja kouvolalaisista vanhainkodeista (osatyö 1). Osallistujat tai lähimmät omaiset (mikäli osallistujan MMSE oli <20) antoivat osallistumisesta kirjallisen suostumuksen. Sisäänottokriteereinä olivat ≥65 vuoden ikä, pysyvä asuminen helsinkiläisessä tehostetun palveluasumisen yksikössä tai kouvolalaisessa vanhainkodissa, suomi äidinkielenä, vähintään yhden lääkkeen käyttö ja odotettu elinikä vähintään 6 kuukautta sekä vapaaehtoinen osallistuminen. Osatyö 1 oli poikkileikkaustutkimus, jossa oli kolmen vuoden kuolleisuuden seuranta. Osatyöt 2-4 perustuivat satunnaistettuun, kontrolloituun tutkimukseen, missä ryhmät satunnaistettiin. Yksiköt satunnaistettiin yksittäisten asukkaiden sijasta, jotta voitiin välttää intervention kontaminoituminen. Resident Assessment Instrument (RAI)-selvityksen perusteella valittiin osastot, joissa oli mahdollisimman samankaltaiset potilasprofiilit (case-mix). Kokonaismäärä oli yhteensä 227 asukasta, heidät satunnaistettiin interventioryhmään (n=118) tai kontrolliryhmään (n=109). Interventiona oli hoitohenkilökunnan koulutusinterventio, joka perustui konstruktiiviseen

oppimisteoriaan. Interventioyksiköiden sairaanhoitajat saivat kahden iltapäivän kestävän koulutuksen ikääntyneiden lääkityksestä, sekä potentiaalisesti haitallisesta että hyödyllisestä. Myös lääkärit olivat tervetulleita koulutukseen. Oppimisprosessi oli aktivoivaa ja siinä hyödynnettiin potilastapauksia. Kontrolliyksiköiden sairaanhoitajat saivat saman koulutuksen 12 kuukauden seuranta-ajan jälkeen. Ensisijainen päätetapahtuma oli tutkittavien osuus, jotka käyttivät haitallisia lääkkeitä sekä muutos haitallisten lääkkeiden käytön lukumäärissä (Beersin lääkkeet, antikolinergiset lääkkeet tai yli 2 psyykelääkettä) Toissijaiset päätetapahtumat olivat muutos terveyteen liittyvässä elämänlaadussa (15D), ja kognitiossa12 kuukauden seurannassa. Lisäksi kaatujien ja kaatumisten lukumäärä sekä terveyspalveluiden käyttö selvitettiin sairaskertomuksista. Kuolleisuutta interventio- ja kontrolliryhmien välillä verrattiin 12 kuukauden ajalta.

Tulokset: Osallistujien ominaisuudet olivat jokseenkin samanlaisia interventio-, kontrolli- ja Kouvola-ryhmissä. Keski-ikä oli 83-84 vuotta, enemmistö, 65-77%, osallistujista oli naisia. Säännöllisiä lääkkeitä oli käytössä keskimäärin yli 7. Charlsonin sairastavuusindeksi (menetelmä, joka laskee sairastavuuden huomioiden kuolemanriskin) oli korkein interventioryhmässä, 3.2, ja matalin Kouvolan ryhmässä, 2.2. Osallistujista 78% käytti jotakin haitalliseksi katsottua lääkettä. Osatyössä 1 oli portaittainen yhteys kolmella eri kriteeristöllä määritettyjen potentiaalisesti haitallisten lääkkeiden (Beersin 2003 lääkkeet, antikolinergisesti vaikuttavat lääkkeet ja >2 psyykenlääkettä) käytön ja terveyteen liittyvän elämänlaadun, henkisen hyvinvoinnin ja itsearvioidun terveydentilan välillä. Mitä useampaan kriteeristöön sisältyviä lääkkeitä oli käytössä, sitä huonompia nämä olivat. Haitallisten lääkkeiden taakka ei ollut yhteydessä kuolleisuuteen 3 vuoden seuranta-aikana.

Kontrolloidussa satunnaistetussa interventiotutkimuksessa intervention ansiosta potentiaalisesti haitallisten lääkkeiden, erityisesti psyykenlääkkeiden, prevalenssi laski merkitsevästi interventioryhmässä (-11.7%, 95% CI -20.5 - -2.9; p=0.009), mutta kontrolliryhmässä muutosta ei tapahtunut (+3.4%, 95% CI -3.7 - 10.6; p=0.34). Elämänlaatu heikkeni merkitsevästi vähemmän interventioryhmässä (-0.038, 95% CI -0.054 - -0.022) kuin kontrolliryhmässä (-0.072, 95% CI -0.089 - -0.055; p=0.005). Interventioryhmän asukkailla sairaalapäivien käyttö oli merkitsevästi vähäisempää verrattuna kontrolliryhmän asukkaisiin, 1.4/henkilö/vuosi (95% CI 1.2 -1.6) versus 2.3/henkilö/vuosi (95% CI 2.1 - 2.7, incidence rate ratio (IRR) interventioryhmälle 0.60, 95% CI 0.49 - 0.75; p <0.001, vakioitu iällä, sukupuolella ja sairastavuudella). Polikliinisten palvelujen käytössä ei ollut eroa. Interventioyksiköiden asukkaat kaatuivat merkitsevästi harvemmin verrattuna kontrolliyksiköiden asukkaisiin. Iällä, sukupuolella ja sairastavuudella vakioitu kaatumisen riski

interventioryhmässä verrattuna kontrolliryhmään oli 0.72 (95% CI 0.59 - 0.88; p<0.001). Kun kaatumisia tutkittiin alaryhmissä, asukkaat, joiden MMSE oli yli 10, hyötyivät eniten interventiosta. Ryhmien välillä ei ollut eroa kielellisellä sujuvuudella tai kellotaululla tutkituissa kognition muutoksissa eikä yhden vuoden kuolleisuudessa.

Johtopäätökset: Eri kriteereiden mukaisten potentiaalisesti haitallisten lääkkeiden taakka liittyi huonompaan elämänlaatuun. Hoitohenkilökunnan koulutus iäkkäiden lääkityksestä onnistui hyvin. Potentiaalisesti haitallisten lääkkeiden, erityisesti psyykenlääkkeiden, käyttöä pystyttiin vähentämään ja kaatumisten määrä ja sairaalahoitopäivien käyttö olivat vähäisempiä interventioryhmässä kuin kontrolliryhmässä. Elämänlaatu heikkeni vähemmän interventioryhmässä kuin kontrolliryhmässä. Kognitioon tai kuolleisuuteen ei kuitenkaan ollut vaikutusta. Myöskään haitallisten lääkkeiden kertymisellä ei ollut vaikutusta kolmen vuoden kuolleisuuteen. Interventio oli aika kevyt ja on todennäköisesti helppo soveltaa muihin samankaltaisiin yksiköihin.

1 Introduction

Older institutionalized residents are often frail. Moreover, they frequently have high numbers of comorbidities, ADL disabilities, and cognitive decline (Onder et al. 2012a). They are thus prone to polypharmacy and adverse effects of drugs (Onder et al. 2012a, 2012b). Furthermore, drug metabolism changes with age, predisposing older people to adverse drug reactions (Mangoni and Jackson 2004). Therefore, medication prescribing to older people has become an important focus in geriatric research as well as a public health issue worldwide (Spinewine et al. 2007).

Several drugs or drug classes have been defined as harmful to older people. Beers' list of inappropriate drugs was the first explicit criteria defining inappropriate medication among nursing home residents (Beers et al. 1991). The list was created by consensus of an expert panel. The Beers' list considered drugs as inappropriate if their adverse effects exceeded the benefits, if they did not have evidence of the desired effects, or if there was a safer alternative available (Beers et al. 1991). Beers' criteria have been updated four times and they cover also home-dwelling older people (Beers 1997, Fick et al. 2003, AGS 2012, AGS 2015). Beers' inappropriate lists are best suited for use in USA, as they include a number of drugs not available in other countries. Many countries have subsequently developed their own prescribing recommendations for older people (Spinewine et al. 2007, Dimitrow et al. 2011, Dimitrow et al. 2013).

Use of drugs with anticholinergic properties (DAPs) is associated with pronounced central and peripheral side effects, such as cognitive decline, delirium, falls, dry mouth, constipation, and urinary retention, among older people (Rudolph et al. 2008, Panula et al. 2009, Gerretsen and Pollock 2011, Viipuri 2016). Due to their marked side effects in older people, the prescribing of anticholinergic drugs requires careful consideration of their benefits and harms (Cardwell et al. 2015). Anticholinergic drugs are included in many lists of inappropriate drugs, but experts have also created their own lists of anticholinergic drugs harmful to older people (Viipuri 2016).

The Omnibus Budget Reconciliation Act of 1987 (OBRA 87) in the USA paid attention to nursing home residents' overuse of psychoactive drugs (Hughes et al. 2005). Older people are especially prone to sedative and other central nervous system adverse effects of psychotropic drugs (Mangoni and Jackson 2004). Psychotropic drugs expose older people to cognitive decline, falls, disabilities, and various other adverse effects (Rosenberg et al. 2012, Pratt et al. 2014). OBRA 87 recommended reducing the use of psychotropic drugs. Antipsychotic drug use in US nursing homes declined after

implementation of this regulation (Garrard et al. 1995). However, atypical antipsychotics and other psychotropic drugs are still widely used in long-term care, especially for neuropsychiatric symptoms associated with dementia, even though there is limited evidence to support their use (Seitz et al. 2013). The Swedish National Board of Health and Welfare (Svenska Socialstyrelsen) has stated that the use of three or more psychotropic drugs simultaneously is harmful to older people (Socialstyrelsen 2010, Socialstyrelsen 2017).

Various harmful drugs for older people have been associated with increased risk of adverse drug events, increased health care usage, and even increased mortality (Gurwitz et al. 2000, Lau et al. 2005, Spinewine et al. 2007). Less is known about how the use of these drugs or drug classes has accumulated among older frail people in institutional settings, and whether reducing the use of these drugs would improve outcomes. Intervention trials have aimed to diminish the use of inappropriate medication in older people (Alldred et al. 2016, Johansson et al. 2016). In many interventions, the use of harmful drugs has decreased (Alldred et al. 2016). However, the effects on other outcomes, such as hospitalizations, falls, quality of life (QOL), and mortality, have been less clear (Alldred et al. 2016, Johansson et al. 2016).

This study examines the accumulation of harmful drugs in institutionalized older people, and the effect of nursing staff education in assisted living facilities on residents' use of potentially harmful drugs and secondary outcomes such as falls, cognition, health-related quality of life (HRQoL), use of health services, and mortality.

2 Review of the literature

2.1 Ageing and medication

2.1.1 Pharmacokinetics and pharmacodynamics

The human body undergoes many age-related changes, which may have effects on pharmacokinetics and pharmacodynamics (Mangoni and Jackson 2004, Boparai and Korc-Grodzicki 2011). Pharmacokinetics refers to the process of absorption, distribution, metabolism, and elimination of a drug in the body, whereas pharmacodynamics comprises the biochemical and physiological effects of drugs (Boparai and Korc-Grodzicki 2011, Rang et al. 2016). Ageing is associated with certain changes in pharmacokinetics (McLean and Le Couteur 2004, Mangoni and Jackson 2004). Also, variability between individuals in physiological responses increases with age (Mangoni and Jackson 2004). Drug metabolism is markedly slower in frail older people than in healthy older people with normal weight (Turnheim 2004, Hubbard et al. 2012).

In the elderly, the secretion of hydrochloric acid and pepsin decreases, but gastric emptying and digestion and motility of the small intestine remain relatively unchanged (Turnheim 2004, Mangoni and Jackson 2004). Thus, the absorption of vitamin B_{12}, iron, and calcium through active transport is reduced, but in general ageing does not notably change drug absorption (Boparai and Korc-Grodzicki 2011). The total body mass and proportion of body water decrease, while the proportion of body fat increases (Mangoni and Jackson 2004, Turnheim 2004, Boparai and Korc-Grodzicki 2011, Hubbard et al. 2012). Thus, distribution volume of hydrophilic drugs decreases (e.g. gentamycin, digoxin, lithium, and theophylline), increasing their concentration. Respectively, the distribution volume of lipid-soluble drugs (e.g. lipophilic benzodiazepines, morphine, lidocaine, thiopental, phenytoin, and verapamil) increases (Boparai and Korc-Grodzicki 2011, Hubbard et al. 2012, Mukhtar and Jackson 2015). Slow release of these drugs from fat storage prolongs the drugs' effect (Hubbard et al. 2012). Diazepam's half-life in adults is about 30 hours, while in older people it is about 90 hours (Boparai and Korc-Grodzicki 2011). Binding of drugs to albumin is not affected during normal ageing, however, frail older people often have lower levels of serum albumin. They are prone to toxicity of acidic drugs, such as warfarin, digoxin, naproxen, ceftriaxone, lorazepam, and valproic acid, which are usually bound extensively to albumin (Boparai and Korc-Grodzicki 2011, Hubbard et al. 2012).

During ageing liver mass and its blood flow decrease, and, as a consequence, the first-pass metabolism slows down (Mangoni and Jackson 2004, Boparai and Korc-Grodzicki 2011). This may increase the bioavailability of many drugs (e.g. propranolol and labetalol). On the other hand, if drugs are pro-drugs and have to be activated in the liver (e.g. enalapril and perindopril), their first-pass metabolism may be slowed down and drug effects reduced (Mangoni and Jackson 2004, Boparai and Korc-Grodzicki 2011).

Many drugs are eliminated through the kidneys (Boparai and Korc-Grodzicki 2011). Glomerular filtration rate (GFR) often decreases in older age, especially if a person has a disease such as hypertension or diabetes that affects renal function (McLean and Le Couteur 2004, Hubbard et al. 2012). As a consequence, this may lead to accumulation of renally cleared drugs (e.g. allopurinol, atenolol, diuretics, digoxin, lithium, water-soluble antibiotics, and NSAIDs) (Mangoni and Jackson 2004, Boparai and Korc-Grodzicki 2011, Mukhtar and Jackson 2015). Use of diuretics may reduce the extracellular space even more, increasing toxic drug effects (Turnheim 2004).

Furthermore, there are pharmacodynamic changes that can increase an older person's sensitivity to medication, especially to drugs that affect the central nervous system (Mangoni and Jackson 2004, Mukhtar and Jackson 2015). The brain weight decreases and the number of synapses decreases (Turnheim 2004). There is an age-related functional decline in the dopaminergic system, which may partly explain why older people are more sensitive to antipsychotic drugs and lower doses are recommended (Turnheim 2004, Uchida et al. 2009). The reduction in acetylcholine may explain older people's sensitivity to anticholinergic side effects (Turnheim 2004). Older people have reduced beta-adrenoceptor function (Mangoni and Jackson 2004, Turnheim 2004), and thus, are less sensitive to the chronotropic effects of isoprenaline (Mangoni and Jackson 2004). Progressive reduction in homeostatic mechanisms is also related to the ageing process. A typical example of this is older people's sensitivity to postural hypotension achieved by blood pressure-lowering drugs (Turnheim 2004, Boparai and Korc-Grodzicki 2011).

2.1.2 Problems related to drug use among older people in institutional settings

Polypharmacy is common in institutional settings (Onder et al. 2012b). While no consensus exists on the definition of polypharmacy, in institutional care it is generally defined as the use of five or more drugs and excessive polypharmacy is defined as 10 or more regular drugs (Onder et al. 2012b). Mean number of drugs among nursing home residents was 7.0-7.1 in Europe, including

Finland, according to the Services and Health for Elderly in long TERm care (SHELTER) study (Onder et al. 2012b). The corresponding figure in Finnish studies was 7.9 in 2003 (Hosia-Randell et al. 2008) and 7.3 in 2011 (Pitkälä et al. 2015).

People living in institutional settings suffer from comorbidities, disabilities, and cognitive decline (Onder et al. 2012a). According to the SHELTER study, the mean age of residents in institutional settings of seven EU countries, including Finland, was above 80 years. More than 80% needed assistance in Activities of Daily Living (ADL), and about 70% suffered from cognitive impairment (Onder et al. 2012a). They also had a high prevalence of urinary incontinence, pain, depression, behavioural symptoms, falls, and pressure ulcers (Onder et al. 2012a). Thus, pharmacological treatment is challenging and often leads to polypharmacy (Onder et al. 2012b). Polypharmacy (use of 5-9 drugs) was observed in 50% and excessive polypharmacy (use of ≥10 drugs) in almost one-quarter of nursing home residents in Europe (Onder et al. 2012b). The use of multiple drugs increases the risk of drug-drug interactions and drug-disease interactions (Onder et al. 2012b).

Excessive polypharmacy has been reported to be associated with malnutrition and a decline in functional and cognitive capacity (Jyrkkä et al. 2011). Excessive polypharmacy was also shown to be associated with depression, falls, pain, dyspnoea, and gastrointestinal symptoms and inversely associated with cognitive impairment and ADL disability (Onder et al. 2012b). In a systematic review, polypharmacy was associated with comorbidity and number of prescribers, while older age, cognitive impairment, ADL disability, and length of stay in long-term care facilities (LTCF) were inversely associated with polypharmacy (Jokanovic et al. 2015).

Polypharmacy was not associated with mortality in a prospective cohort study with a 2-year follow-up (Schlesinger et al. 2016). However, excessive polypharmacy was associated with one-year mortality among cognitively impaired nursing home residents (Onder et al. 2013), and, according to a cohort study, with 10-year mortality in older people aged ≥75 years (Jyrkkä et al. 2009).

2.2 Potentially harmful medications (PHMs) for older people

Appropriate prescribing for older people is challenging. Adverse drug effects may lead to excess health care use and hospitalizations (Hanlon et al. 1997, Lau et al. 2005, Perri et al. 2005, Price et al. 2014). The quality of prescribing drugs has been defined in several ways. Often older people may not receive all the drugs that their disease or condition requires (underprescribing). Alternatively, older people may get more drugs than are clinically indicated (overprescribing), or

they may even receive incorrectly prescribed drugs (misprescribing) (Spinewine et al. 2007). Poor quality of prescribing raises health care costs significantly (Fick et al. 2003).

Experts in many countries have developed their own criteria for potentially inappropriate drugs to improve older people's drug treatment (Dimitrow et al. 2011). These criteria can be defined as implicit or explicit (Spinewine et al. 2007). Explicit criteria are drug- or disease-oriented, and they give instructions to avoid certain drugs that can be potentially harmful for older people (Beers et al. 1991). Implicit criteria are more patient-oriented and based on tailored clinical judgements about appropriateness (Spinewine et al. 2007).

2.2.1 Various criteria for inappropriate prescribing

Various criteria for inappropriate medications are summarized in Table 1.

Overuse of psychotropics in nursing homes received much attention already in 1987 in the USA (OBRA 87). Four years later, geriatrician Mark Beers and colleagues were the first to develop explicit criteria with the aid of an expert panel for drugs that are inappropriate for nursing home residents (Beers et al. 1991). In Beers' criteria, drugs are considered inappropriate if their unwanted effects exceed their benefits, if they lack efficacy, or if there is safer alternative available (Beers et al. 1991). Beers' criteria were based on American practices. Beers' list has been extended to community-dwelling older people and updated four times since the first panel's work (Beers 1997, Fick et al. 2003, AGS 2012, AGS 2015). Beers' lists are the most commonly used criteria for inappropriate drugs. However, Beers' criteria have been criticized for including a large proportion of medications that are not available in other countries (O'Mahony et al. 2010). Beers' criteria have also been criticized for not taking into account drug-drug interactions and duplicate drug classes. Furthermore, both the Beers' lists of drugs independent of diagnoses and drugs related to certain conditions were criticized for being in a random order (O'Mahony and Gallagher 2008). They also lacked recommendations for often under-prescribed evidence-based medications for older people.

In Canada, McLeod and colleagues created their own national recommendations for older people's medication. The consensus panel of 32 specialists in clinical pharmacology, geriatrics, family medicine, and pharmacy used a modified Delphi method and identified 38 inappropriate practices in prescribing to older people. Inappropriate prescribing had to meet three criteria: increase in the potential risk of serious adverse effect, more effective or less risky alternative therapy was available, and change of practice could decrease morbidity of older people. These practices were

divided into four groups: prescribing to treat cardiovascular diseases, psychotropic drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics, and others. Of these practices, 18 were generally contraindicated in older people, 16 involved drug-disease-interaction, and four involved drug-drug-interactions. Three of these four drug-drug interactions were related to oral warfarin use (McLeod et al. 1997).

Zhan with colleagues gathered an expert panel in the USA consisting of seven experts in geriatrics, pharmaco-epidemiology, and pharmacy. They categorized potentially inappropriate medication for community-dwelling older people (Zhan et al. 2001). Their list was based on 1997 Beers' criteria. A modified Delphi method with two rounds was used. The panel classified 33 drugs into three categories: 11 drugs that should always be avoided, 8 drugs that are rarely appropriate, and 14 drugs that have some indications but are often misused among community-dwelling older people. For example, diazepam was included in the "rarely appropriate list". The panel believed that long-acting benzodiazepines were mostly inappropriate. However, diazepam and chlordiazepoxide could be used for a short treatment course for alcohol withdrawal. Amitriptyline was in the "some indications" category; the panel's consensus was that it could be used in low doses for the treatment of neuropathic pain, but it should not usually be used for treatment of depression (Zhan et al. 2001).

A French consensus panel created their own list of inappropriate medications for older people (Laroche et al. 2007). It included 34 criteria applicable to people ≥75 years, comprising 29 medications or medication classes for all patients and 5 for specific medical conditions. According to this list, NSAIDs, for instance, were allowed, except for indomethacin and phenylbutazone or simultaneous use of two or more NSAIDs. Many anticholinergic psychotropics were not allowed, but meprobamate was allowed as an alternative drug, but not for gastrointestinal dysfunction. The list of inappropriate drugs consisted of anticholinergic antihistamines, muscle relaxants, and antispasmodics, and simultaneous use of drugs with anticholinergic properties was discouraged. Long-acting benzodiazepines, centrally acting antihypertensives, and short-acting calcium-channel blockers were included in the list, as was digoxin > 0.125 mg/d. However, contrary to Beers' list (Fick et al. 2003), amiodarone was allowed. There were also medication recommendations for certain clinical conditions and two warnings for drug-drug interactions as follows: simultaneous use of two or more psychotropic drug from the same therapeutic class and simultaneous use of cholinesterase inhibitor drugs and drugs with anticholinergic properties (Laroche et al. 2007).

In Ireland, an 18-member expert panel using a Delphi consensus method developed the STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria (Gallagher et al. 2008, O'Mahony et al. 2010).

Experts from geriatric medicine, clinical pharmacology, clinical pharmacy, old age psychiatry, and primary care created 65 STOPP criteria (drugs to avoid) and 22 START criteria (drugs indicated in certain conditions). STOPP criteria were arranged according to physiological systems, e.g. cardiovascular system, central nervous system and psychotropic drugs, gastrointestinal system, respiratory system, musculoskeletal system, urogenital system, and endocrine system. In addition, drugs causing adverse effects such as falls, analgesic drugs having high risk of adverse effects, and medications from duplicate drug classes were advised to be avoided. Contrary to Beers' criteria, there were also START criteria for drugs considered indicated for older people in certain conditions, such as warfarin in the presence of atrial fibrillation. Recommendations were also made for respiratory, central nervous, gastrointestinal, musculoskeletal, and endocrine system medications (Gallagher et al. 2008, O'Mahony et al. 2010). The STOPP criteria covered many drugs not mentioned in Beers' criteria. For example, there was a recommendation to avoid NSAIDs with moderate-severe hypertension, with heart failure, and with chronic renal failure. In addition, the criteria advised not using PPIs at full therapeutic dose for more than 8 weeks when treating peptic ulcer. It has been suggested that the STOPP criteria might be more helpful than Beers' criteria to identify potentially inappropriate medications that may lead to acute hospitalizations (Gallagher and O'Mahony 2008). STOPP and START criteria have been updated in 2015 (O'Mahony et al. 2015). This new version contains 80 STOPP criteria and 34 START criteria. The new STOPP criteria were antiplatelet/anticoagulant drugs, drugs affecting renal function, and drugs that may increase anticholinergic burden. The new START criteria included new categories of drugs such as medications for the urogenital system, analgesics, and vaccines. Fifteen of the criteria from STOPP/START version 1 (Gallagher et al. 2008, O'Mahony and Gallagher 2008) are not included in STOPP/START version 2 (O'Mahony et al. 2015).

Because of the severity of medication-related problems, there was a need for local recommendations based on Australian data (Basger et al. 2008). Beers' list was not appropriate for the Australian health care environment. Prescribing indicator tools were developed after examining the most common reasons for older Australians seeking or receiving health care (Basger et al. 2008) and cross-referencing these with the 50 highest-volume Pharmaceutical Benefits Scheme medications prescribed. They identified a total of 48 indicators. Eighteen indicators concerned

avoidance of medications in certain conditions or diseases and 19 concerned recommended treatment in certain conditions or diseases. There were also indicators for medication monitoring, specific drug interactions, questions about any changes in medication in the previous 90 days, smoking, and vaccination status (Basger et al. 2008).

Furthermore, Norwegian researchers created their own criteria to suit their practices for older people (Rognstad et al. 2009). The Norwegian General Practice (NORGEP) criteria for potentially inappropriate medication were developed as explicit criteria to be used in general practice for home-dwelling older people (>70 years). It included 36 drugs, drug dosages, and drug combinations to be avoided for safety reasons. There were such drugs as tricyclic antidepressants, conventional antipsychotics, long-acting benzodiazepines, theophylline, sotalol, and first-generation antihistamines. Combinations to be avoided among older people included warfarin with NSAIDs, or selective serotonin reuptake inhibitors (SSRIs) with certain quinolones or macrolides. According to these criteria, NSAIDs or coxibs should not be used with angiotensin converting enzyme (ACE) inhibitors, diuretics, glucocorticoids, or SSRIs. There was also a recommendation not to simultaneously use three or more drugs belonging to the groups of centrally acting analgesics, antipsychotics, antidepressants, and benzodiazepines (Rognstad et al. 2009).

Norwegians also developed their own explicit criteria for inappropriate medication for nursing home residents aged >70 years (Nyborg et al. 2015). These Norwegian General Practice Nursing Home (NORGEP-NH) criteria for potentially inappropriate medication were created by a three-round consensus process using the Delphi technique. The panel consisted of geriatricians, general practitioners, and clinical pharmacologists. NORGEP-NH included many of the same medications as NORGEP, but, for example, zopiclone was recommended to have a maximum dose of 5 mg instead of 7.5 mg. There were also recommendations for critical assessment of continuing antipsychotics, antidepressants, urologic spasmolytics, anticholinesterase inhibitors, antihypertensives, bisphosphonates, statins, and any preventive medications.

The Swedish National Board of Health and Wellfare developed its own indicators for older people's medication. These were published for the first time in 2004 and updated in 2010 and 2017 (Socialstyrelsen 2010, Socialstyrelsen 2017). The recommendations were targeted to older people (≥75 years) and based on the international literature. There were 9 drug-specific and 11 disease-specific indicators. Drug-specific indicators were defined and categorized as follows: 1. Drugs to be avoided among people ≥75 years unless there is a specific indication for their use. The expected benefit of the drug should exceed the risks. These drugs include long-acting benzodiazepines such

as diazepam or nitrazepam, drugs with anticholinergic properties, and tramadol. 2. Preparations for which a correct and current indication is of particular importance. These include drugs that are quite commonly prescribed and often without a clear indication. There is a risk for adverse effects. These include medications such as NSAIDs, paracetamol (acetaminophen), opioids, antipsychotics, proton pump inhibitors (PPIs) and SSRIs. 3. Drugs that often are used regularly, although they should be used only for a short period of time like hypnotics, bowel-stimulating laxatives, NSAIDs, oral glucocorticoids, and antipsychotics. 4. Avoiding overdosing of some drugs. For example, risperidone should not be used >1.5 mg/day among people ≥75 years, oxazepam not >30 mg/day, and zopiclone not >7.5 mg/day. 5. Warning for polypharmacy: older people should not use ≥10 drugs at the same time, regularly or pro re nata (as needed). There is a risk for side effects, drug-drug interactions, and difficulties in complying with the instructions. Also simultaneous use of two or more drugs of the same drug class, like two or more opioids or two benzodiazepines, may be inappropriate. Sometimes this is necessary and justified, e.g. two or more antiparkinson drugs or combinations of antidepressants. Simultaneous use of three or more psychotropics is also considered to be inappropriate because there is risk for drug-drug interactions and side effects. 6. Combinations of drugs that may lead to clinically significant drug-drug interactions (D-class interactions), e.g. the combination of warfarin and NSAID. 7. Drugs for which use or dosing must be adjusted according to renal function, e.g. digoxin and potassium-sparing diuretics. 8. Drugs leading to side effects like orthostatic hypotension or increasing the risk for falls or impaired cognition. 9. There were also recommendations on the hypnotics and sedatives to be avoided and others specified that are safer to use. There were also 11 different recommendations according to diagnoses, e.g. hypertension, ischaemic heart disease, heart failure, diabetes, sleeping problems, and chronic obstructive pulmonary disease (COPD) (Socialstyrelsen 2010).

In Finland, there is the Meds75+ database that describes inappropriate and appropriate medications for older people (Fimea 2016). Fimea (Finnish Medicines Agency) operates under the Ministry of Social Affairs and Health of Finland. Its aim is to maintain and improve the health of the population by supervising and developing the pharmaceutical sector. The database, available since 2010, is primarily intended for physicians and other health care professionals, and its purpose is to support the clinical decision-making on the pharmacotherapy of people ≥75 years and to improve medication safety in primary health care. A team of pharmacotherapy experts developed the database, which is currently being updated; the first part of the update was published in 2013 and the update is ongoing. Medicinal substances are classified into the categories A (green), B (grey), C

(yellow), and D (red). The category indicates how suitable the medicinal substance is for people ≥75 years. The categories are based on a multidisciplinary clinical consensus (Fimea 2016).

Category A medicinal substances are appropriate for older people and can be used similarly as in younger patients. Category B includes medicinal substances for which there is little scientific evidence, practical experience, or efficacy in persons over 75 years of age. Category C medicinal substances can be used for older people, but the dose might either have to be reduced or the frequency of administration decreased due to mild or moderate renal insufficiency or a significant risk of interactions or adverse reactions. Category D medicinal substances should be avoided in older people. They can be used only in exceptional cases or on a one-off basis. Changes due to ageing predispose older people to adverse or dangerous reactions to these substances. The risk of adverse reactions typically exceeds potential benefits. In individual cases, the use of category D medicinal products can be considered. The drug information on each pharmaceutical substance contains information on the effects and dosing of the substance and the most typical adverse reactions and interactions, e.g. whether the drug has anticholinergic, serotonergic, or sedative side effects. Indications and contraindications are not mentioned.

Leikola and colleagues in Finland developed a Comprehensive Medication Review (CMR) procedure to improve pharmacotherapy among community-dwelling older people (Leikola 2012). The CMR includes a review of the literature and medication review procedures and pilot testing by experienced pharmacists. Inappropriate drugs are based on Beers' criteria. Pharmacists receive special training in order to qualify for CMR. The procedure includes clinical patient information, a home visit with patient interview, discussion with the collaborating physician, and documentation. The focus is on inappropriate drugs, undertreatment, and adequate treatment of pain.

In Finland, a tool for practical nurses working in home care has also been developed to recognize drug-related problems (Dimitrow 2016). A three-round Delphi survey with a panel of 18 experts validated the draft tool. The final Drug-Related Problem-Risk Assessment Tool (DRP-RAT) contains 18 items, focusing on both DRPs related to pharmacology and the medicine use process. Recommendations to solve problems are also included (Dimitrow 2016).

In addition to many explicit criteria (Beers et al. 1991, Beers 1997, Laroche et al. 2007) and explicit-implicit criteria (Gallagher et al. 2008), also implicit criteria have been created to evaluate the appropriateness of medication prescribed to older people (Hanlon et al. 1992). This Medication Appropriateness Index (MAI) consists of 10 criteria in question form to consider when evaluating a

prescribed drug. The questions are the following: 1. Is there an indication for the drug? 2. Is the medication effective for this condition? 3. Is the dosage correct? 4. Are the directions correct? 5. Are the directions practical? 6. Are there clinically significant drug-drug interactions? 7. Are there clinically significant drug-disease/condition interactions? 8. Is there unnecessary duplication with other drugs? 9. Is the duration of therapy acceptable? 10. Is this drug the least expensive alternative compared to others of equal utility? The MAI is calculated according to the answers to these questions (Hanlon et al. 1992). The MAI may be useful for research studies, quality improvement, and patient care (Samsa et al. 1994).

See Table 1.

Table 1. Criteria for potentially harmful drugs for older people. Explicit criteria=medications defined as potentially inappropriate according to different criteria. Implicit criteria=clinical judgement of appropriateness.

Publication, country	Target group	How the list was developed	Definition and contents of criteria	Comments
Criteria for potentially harmful drugs for older people, explicit				
Beers criteria				
Beers et al. 1991, USA	Nursing home population	Expert panel	30 criteria, 19 that should generally be avoided and 11 that had limitations on doses, frequencies, or duration of use	13 nationally recognized experts
Beers 1997, USA Update 1	Older people >65 years	Expert panel	28 criteria of medications generally to be avoided and 35 criteria in older people related to 15 medical conditions	6 nationally recognized experts
Fick et al. 2003, USA Update 2	Older people ≥65 years	Expert panel	48 medications or medication classes to be avoided, and medications to be avoided in relation to 20 conditions	66 PIDs were considered to have very serious adverse outcomes
AGS 2012, USA Update 3	Older people ≥65 years	Expert panel	Beers' 2012 list consists of 53 medications or medication classes divided into three categories: 1. Medications or medication classes to be avoided among older people, 2. Medications or medication classes related to certain conditions, 3. Medications to be used with caution among older people	
AGS 2015, USA Update 4	Older people ≥65 years, except hospice and palliative care	Expert panel	Only three new medications in list drug and drug classes or related to conditions. As new, a list of drugs needing adjustment according to renal function and a list of drug-drug interactions	Drug-drug interaction list is selective, not comprehensive
Other explicit criteria				
McLeod et al. 1997, Canada	Older people >65 years	Expert panel	38 practices; 16 generally contraindicated, 11 involving drug-drug interactions, and 11 involving drug-disease interactions	Rating scale from 1 to 4
Zhan et al. 2001, USA	Home dwelling ≥65 years	Expert panel	33 inappropriate medications; 11 should always be avoided, 8 are rarely appropriate, and 14 have some indications	Patients with poor health and more medications more often have inappropriate medications
Laroche et al. 2007, France	Older people ≥75 years	Expert panel	34 criteria; 29 medications to be avoided and 5 medications to be avoided in certain conditions	5-point Likert scale
Rognstad et al. 2009, Norway	Older people >70 years in general practice	Expert panel	36 explicit criteria; 21 single drugs and dosages, 15 combinations to be avoided	Partly based on Beers' criteria

Table 1. Continued…

Nyborg et al. 2015, Norway	Older people >70 years in nursing homes	Expert panel	34 criteria; 11 single drugs and their dosages, 15 drug combinations, and 8 drug groups for which continued use requires reassessment	
Fimea 2016 Hartikainen and Ahonen, Finland	Older people ≥75 years	Team of pharmacotherapy experts	Drugs classified as A (green), B (grey), C (yellow), and D (red)	Multidisciplinary clinical consensus. Information on the effects and dosing, adverse reactions and interactions, not indications or contraindications
Dimitrow 2016, Finland	Home care patients ≥65 years	Expert panel	Development and validation of Drug-Related-Problems-Risk Assessment Tool (DRP-RAT) for practical nurses working in home care	18 experts in geriatric care and pharmacotherapy in expert panel
Criteria for potentially harmful drugs for older people, including both explicit and implicit criteria				
Gallagher et al. 2008, Ireland	All people ≥65 years	Expert panel	65 system-based criteria to stop use of inappropriate drugs, 22 system-based criteria to start a certain medication	Concerns also evidence-based medication start among older people
Basger et al. 2008, Australia	Older people >65 years	Most common problems, hospital admissions, and medical conditions considered	48 indicators; 18 to avoid and 19 to recommend medications in certain conditions, and other recommendations	All required information from Australian information sources. Not involving expert consensus process
Socialstyrelsen 2010, Socialstyrelsen 2017, Sweden	Older people ≥75 years	Literature review, expert opinion	In 2010 9 drug-specific and 11 disease specific recommendations, in 2017 9 drug-specific and 13 disease specific recommendations	Concomitant use of >2 psychotropic drugs is considered to be inappropriate
Leikola 2012, Finland	Home-dwelling older people ≥65 years	Literature review, pilot testing	Comprehensive Medication Review (CMR) procedure. Inappropriate medication according to Beers' criteria 2003, also attention to possible undertreatment and pain treatment, collaborating with physician	Pharmacists received special training to qualify for CMR
O'Mahony et al. 2015, Ireland		Expert panel	80 system-based criteria to stop use of inappropriate drugs, 34 system-based criteria to start a certain medication	Update from stop and start 2008 version
Criteria for potentially harmful drugs for older people, implicit				
Hanlon et al. 1992, Samsa et al. 1994, Hanlon and Schmader 2013, USA	Older people >65 years	Sample of 10 academic health care professionals	Ten questions to answer: on indication, effectiveness, dosage, correct directions, drug-drug interactions (DDI), drug-disease interactions, practicality, costs, duplications, and duration of therapy. Questions are answered A "appropriate", B "marginally appropriate", or C "inappropriate" and summed according to a weighting system to yield the Medication Appropriateness Index (MAI)	

AGS=American Geriatrics Society; PID=potentially inappropriate drug

2.2.2 Beers' inappropriate drugs

Polypharmacy was common already in the 1990s among institutionalized older people in the USA. According to a well-known study, nursing home residents were prescribed on average eight medications and more than half of the residents were on psychotropics and one in four on antipsychotics (Beers et al. 1988). There was a need for criteria to define appropriateness of medication for older persons. To help overcome differences in published opinions, a panel of experts defined the first Beers' inappropriate drugs for older people (Beers et al. 1991). The best criteria were considered to result from the consensus of experts in the fields of geriatric medicine, geropsychiatry, and geriatric pharmacology, guided by published statements (Beers et al. 1991). The criteria were based on a comprehensive literature review (Beers et al. 1991).

2.2.2.1 Development of Beers' list over decades

Differences in medications between Beers' lists 2003, 2012, and 2015 are presented in Appendix 1.

There were 30 drugs/drug categories to be avoided in the first Beers' criteria such as sedative-hypnotics, antidepressants, antipsychotics, antihypertensives, non-steroidal anti-inflammatory agents, oral hypoglycaemics, analgesics, dementia treatments, platelet inhibitors, histamine 2 blockers, antibiotics, decongestants, iron supplements, muscle relaxants, gastrointestinal antispasmodics, and antiemetics. Of these, 19 should always be avoided and 11 received recommendations for dose, frequency, or duration of treatment (Beers et al. 1991).

The first Beers' criteria were updated in 1997. The new recommendations concerned all older people (≥65 years) regardless of where they lived (Beers 1997). Beers' criteria 1991 identified inappropriate medication use in nursing homes in the absence of clinical information on diagnoses. When Beers' criteria were updated, there was a database available with more information on older people's diagnoses and conditions. The revised criteria consisted of 28 criteria describing the potentially inappropriate use of older people's medication. There were also 35 criteria defining potentially inappropriate medication use in older persons related to 15 common medical conditions. In Beers' 1997 criteria, a new term "potentially inappropriate medication" (PID) instead of "inappropriate medication" appeared for the first time. In the original article (Beers 1997), Beers presented criteria for potentially inappropriate drugs related to 19 conditions, e.g. patients with heart failure should not receive disopyramide or drugs with high sodium content, patients with

ulcers should not receive NSAIDs, Aspirin >325 mg, or potassium supplements, and patients with peripheral vascular disease should avoid β-blockers.

The next Beers' criteria update was published in 2003 (Fick et al. 2003). Recognition of medication-related problems was considered important because these problems were thought to increase hospital admissions, costs, and even deaths (Hanlon et al. 1997, Lazarou et al. 1998). New drugs had been released, knowledge about older drugs had increased, and drugs had been removed from the market, so it was time to update the criteria for potentially inappropriate drugs among older people. Beers' criteria 2003 consisted of 48 medications or classes of medications that should be avoided or limited in their doses or duration of treatment in older persons. In the Beers' update 2003, there was also a list of 20 diseases or conditions and medications to be avoided when treating older adults with these conditions. New conditions comprised depression, cognitive impairment, Parkinson's disease, anorexia, malnutrition, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and obesity.

Fifteen medications or medication classes were dropped from the list compared with Beers' 1997 criteria. Most of the dropped medications were related to certain conditions. These included recently started corticosteroid therapy with diabetes, β-blockers with diabetes, asthma, peripheral vascular disease, and syncope and falls. Furthermore, sedative-hypnotics with COPD, potassium supplements with gastric or duodenal ulcers, metoclopramide with seizures or epilepsy, narcotics with bladder outflow obstruction or constipation, desipramine, SSRIs and β–agonists with insomnia, and bethanechol chloride with bladder outflow obstruction were excludedfrom the list. Guidelines changed as follows: reserpine should be avoided only at doses >0.25 mg, oxybutynin was considered safe in its extended-release form, and dipyridamole should be avoided only in its short-acting form.

Compared with the previous update, 25 drugs or drug classes independent of diagnoses were added like ketorolac, orphenadrine, nitrofurantoin, clonidine, cimetidine, ferrous sulphate, amphetamines, short-acting nifedipine, daily fluoxetine was included again in PIDs, stimulant laxatives except when using opioids simultaneously, amiodarone, NSAIDS such as naproxen, oxaprozin, and piroxicam, oestrogens in older women, methyltestosterone, and mesoridazine (Fick et al. 2003). In addition, the criteria included 19 medications or medication classes to be avoided related to certain conditions such as benzodiazepines and tricyclic antidepressants with falls, barbiturates, antispasmodics, and muscle relaxants with cognitive impairment, and metoclopramide,

conventional antipsychotics, and tacrine with Parkinson disease (Fick et al. 2003). Appendix 2 presents a list of Beers' drugs 2003 available in Finland in 2011 as well as their drawbacks.

The Beers' criteria have been criticized for including a high number of medications not available in European countries (O'Mahony et al. 2010). The earliest lists also failed to include many psychotropics that can cause adverse effects.

Potentially inappropriate medications (PIMs) were still commonly used among vulnerable older adults, and it was again necessary to update recommendations for medication for older people. Updating was realized with the support of the American Geriatrics Society. Consensus was reached after a systematic literature review by a panel of 11 specialists in geriatric care and pharmacotherapy (AGS 2012). In the AGS 2012 criteria, medications were divided into three categories: PIMs and classes to avoid among older adults; PIMs and classes to avoid among older adults related to certain conditions; and medications to be used with caution among older adults. The 2012 AGS Beers' criteria were, like the two previous criteria, intended to be used among all people aged 65 years or older regardless of where they live. In this updating, the quality of evidence was estimated to be as high-moderate-low and the strength of the recommendation as strong-weak-insufficient. Most of the estimations for quality of evidence were moderate or high, and most of the recommendations were strong (AGS 2012).

There were 34 potentially inappropriate medications or medication classes to be avoided among all older people aged 65 years or more. Differences between Beers' list 2003 and Beers 2012 in medications independent of diagnoses or conditions are presented in Appendix 1. A notable difference was that there were altogether 16 NSAIDs in oral use to be avoided in the new list. Benzodiazepines should always be avoided; there were no more maximum doses. There were also 12 conventional antipsychotics and 10 atypical antipsychotics that should be avoided. This recommendation was based on studies suggesting risk of antipsychotic use, which may cause strokes and even deaths in persons with dementia (AGS 2012). New potentially inappropriate drugs were, for example, spironolactone >25 mg/d, testosterone, oestrogens also with progestins, oral aspirin >325 mg/d, megestrol, glyburide, and sliding scale insulin therapy.

New drugs added to the list related to certain conditions were, for example, glitazones with heart failure, acetylcholinesterase inhibitors with a history of syncope, and SSRIs with falls and fractures (AGS 2012). There was also a list of medications that should be used with caution among older people. For example, aspirin for primary prevention of cardiac events among people ≥80 years was

not evidence-based, vasodilators should be used with caution because they may cause syncope, and when using SSRIs, sodium level should be monitored.

The latest Beers' criteria update was published in 2015 (AGS 2015). The criteria were applicable to all individuals aged 65 years or more, except those in hospice and palliative care. Compared with the 2012 criteria, there were only a few changes in these lists. Antiarrhythmic drugs, except disopyramide and dronedarone, were removed, and amiodarone and digoxin were advised to be avoided as first-line treatment for atrial fibrillation. Constipation was removed from the "according to certain conditions list". Proton pump inhibitors (PPIs) should not be used for more than 8 weeks unless for high-risk patients because of an association between the use of PPIs and *Clostridium difficile* infection, bone loss, and fractures. Desmopressin was added to an independent list of conditions (incontinence) for risk of hyponatremia and first-generation antihistamine meclizine to the anticholinergic list. The hypnotics eszopiclone and zaleplon should be avoided in patients with dementia or cognitive impairment. Antipsychotics should be avoided as first-line treatment in delirium. Some medications, such as nitrofurantoin, were moved to another category or modified. Nitrofurantoin can be used with caution also in individuals with creatinine clearance ≥30 ml/min (vs. the earlier ≥60 ml/min), but only in the short term.

A new list in the 2015 Beers' criteria included drug-drug interactions (excluding anti-infectives). This list was selective and not comprehensive. An example from this list is a recommendation for not using more than two central nervous system drugs concomitantly. Concomitant use of warfarin with NSAIDs was also forbidden (AGS 2015). Potentially inappropriate medications based on renal function were also on the new list. There were medications that should be avoided or for which the dose should be adjusted according to decreased renal function such as amiloride, triamterene, some non-vitamin K antagonist oral anticoagulants, duloxetine, and famotidine (AGS 2015).

See Appendix 1.

2.2.2.2 Prevalence of Beers' drugs in institutional settings

The prevalence of PID use in institutional settings is presented in Table 2.

Of home care patients (≥65 years) in eight European countries, 20% used inappropriate medication according to three different criteria (Beers' lists 1997 and 2003, and McLeod's list 1997) (Fialová et al. 2005). The highest prevalence was in the Czech Republic, 41%, and the lowest in Denmark,

6% (Fialová et al. 2005). According to a cross-sectional study (data from 1 November 1998 to 31 March 1999 in Finland), 13% of 3219 home-dwellers used inappropriate medication from Beers' list 1997 (Pitkälä et al. 2002a). According to register-based data from 2007, the use of Beers' criteria 2003 PIDs among all home-dwelling older people was still quite low in Finland, 15% (Leikola et al. 2011). In Italy, the prevalence of the use of Beers' 2003 PIDs among the community-living 80+ years population was 26% (Landi et al. 2007).

Use of Beers' inappropriate drugs was common also among community-dwelling older people in USA. According to a retrospective cohort study, 40% used one and 13% two or more Beers' drugs (Fick et al. 2008). According to a recent American study, 43% of community-dwelling adults aged ≥65 years used Beers' 2012 inappropriate drugs, NSAIDs being the most common (11%) (Davidoff et al. 2015). Based on a systematic review, the use of PIMs varied markedly in studies in 1997-2009, from 12% to 63% (Guaraldo et al. 2011). PIMs were defined using Beers' criteria/other criteria derived from Beers (Guaraldo et al. 2011).

According to a retrospective cohort study, 40% of US nursing home residents used Beers' 1991 inappropriate medication, 10% used two or more, and 7% of all prescriptions were inappropriate (Beers et al. 1992). From almost 20 000 nursing home residents, 49% used inappropriate medication in USA during a one-year follow-up (Gupta et al. 1996). Of nursing home residents (N=20 573), 33% were on inappropriate medication, whereas among community-dwelling persons (N=44 259) the respective figure was 24% (Piecoro et al. 2000). Dhall and colleagues (2002) investigated in USA how the use of PIDs changed during the 90 days after admission to a nursing home. At admission, 33% of residents received at least one PID; during the following 90 days the drug was discontinued in 16% of these residents. Among those not receiving any PID initially, medication commenced in 18% (Dhall et al. 2002). Later, the prevalence of inappropriate medication has varied between 26% and 50% in USA (Briesacher et al. 2005, Lau et al. 2004, Rigler et al. 2005). The highest prevalence of 50% was found in a study in which also PIDs according to conditions were considered (Lau et al. 2004). Comparing the prevalence in 1997 versus 2000 among nursing home residents, the use of PIDs had decreased from 29% to 26% and in assisted living facilities from 22% to 19% (Briesacher et al. 2005). A study investigated the effect of implementing the modified updated Beers' criteria in nursing homes on the use of inappropriate medication among nursing home residents in USA. The use of any PIM decreased from 43% in 1997 to 40% in 2000, resident characteristics adjusted Odds ratio (OR) = 0.85, 95% CI 0.84 to 0.87) (Lapane et al. 2007).

The use of potentially inappropriate medication among older people is also common in institutional settings in other countries. In Finland, approximately one-third of the residents in nursing homes were on PIDs (Raivio et al. 2006, Hosia-Randell et al. 2008). In Italy, almost half of the residents in nursing homes were exposed to PIDs according to the Beers' 2003 list (Ruggiero et al. 2010). Of residents in long-term care facilities in Japan, 21% used PIDs according to a diagnosis-independent list and 18% according to a certain conditions list (Niwata et al. 2006).

In Tasmania, Australia, 35% of residential care home residents used at least one Beers' criteria 2003 medication and females more often received inappropriate psychotropic medication (Stafford et al. 2011). Compared with potentially inappropriate medication according to McLeod's criteria (19%), Beers' criteria identified more inappropriate drugs (Stafford et al. 2011). Some years later, the use of PIDs was still high in Australia (55%) (Bosboom et al. 2012). In Malaysia, 33% of 211 nursing home residents used PIDs according to Beers' 2003 criteria, whereas the proportion of PIDs was 24% according to STOPP criteria (Chen et al. 2012). The highest prevalence of PIDs among nursing home residents was found in Brazil, 83% (Vieira de Lima et al. 2013).

See Table 2.

Table 2. Prevalence of Beers' potentially inappropriate drugs (PID) in institutional settings.

Study	**Country**	**Setting**	**N/ Females %**	**Age, years**	**Beers' criteria**	**Prevalence %**
Beers et al. 1992	USA	NH	1106/80%	84	1991	40
Gupta et al. 1996	USA	NH	19932/74%	60% >80	1991	49
Piecoro et al. 2000	USA	NH	20573	≥65	1997	33
Dhall et al. 2002	USA	NH	29062/69%	82% ≥75	1997	33
Lau et al. 2004	USA	NH	3372/74%	≥65	1991, 1997	50
Perri et al. 2005	USA	NH	1117/82%	85	1997	47
Rigler et al. 2005	USA	NH	1164/77%	82% >75	1997	38
Niwata et al. 2006	Japan	LTCF	1669/75%	85	2003	21
Raivio et al. 2006	Finland	NH+AH	425/82%	86	2003	36
Lapane et al. 2007	USA	NH	1997 130250/72% 2000 164889/70%	77% ≥75 74% ≥75	1991 and 1997	43 40
Hosia-Randell et al. 2008	Finland	NH	1987/81%	84	2003	35
Ruggiero et al. 2009	Italy	NH	496/75%	82	2003	17
Ruggiero et al. 2010	Italy	NH	1716/72%	84	2003	48
Stafford et al. 2011	Australia	RCH	2345/76%	63% ≥85	2003	35
Bosboom et al. 2012	Australia	RAFC	226/75%	86	2003	55
Chen et al. 2012	Malaysia	NH	211/61%	78	2003	33
Vieira de Lima et al. 2013	Brazil	LTCF	261/58%	>60, 22% ≥85	2012	83

AH= Acute Hospitals; CMS = Centers for Medicare and medicaid Services; LTCF= Long-Term Care Facilities; NH= Nursing Homes; RACF= Residential Aged Care Facilities; RCH= Residential Care Homes

2.2.2.3 Factors associated with use of Beers' drugs

The use of Beers' inappropriate drugs has been associated with polypharmacy (Dhall et al. 2002, Pitkälä et al. 2002a, Lau et al. 2004, Fialová et al. 2005, Perri et al. 2005, Niwata et al. 2006, Raivio et al. 2006, Landi et al. 2007, Hosia-Randell et al. 2008, Ruggiero et al. 2010, Guaraldo et al. 2011, Stafford et al. 2011, Chen et al. 2012, Vieira de Lima et al. 2013). Residents who were administered psychotropics more often received PIDs (Fialová et al. 2005, Niwata et al. 2006, Hosia-Randell et al. 2008, Stafford et al. 2011).

Some studies showed that the use of PIDs was associated with younger age (Piecoro et al. 2000, Ruggiero et al. 2010), whereas others reported an association with older age (Landi et al. 2007, Lin et al. 2008, Cahir et al. 2014). White race (Piecoro et al. 2000), female sex (Beers et al. 1992, Piecoro et al. 2000, Dhall et al. 2002, Guaraldo et al. 2011, Cahir et al. 2014), poor economic situation, and living alone (Fialová et al. 2005) were associated with the probability of receiving inappropriate medication.

Multivariate analysis showed that residents living in larger nursing homes received more inappropriate medications than those living in smaller nursing homes (Beers et al. 1992). The risk of receiving inappropriate drugs decreased when living in a smaller nursing home (number of beds <100) and in nursing homes with a higher ratio (≥1/20) of registered nurses/residents (Lau et al. 2004). Use of Beers' drugs was associated with longer nursing home stays (Chen et al. 2012).

One prospective cohort study showed an association of PID use with cognitive impairment (Landi et al. 2007), whereas most studies have found no association with dementia (Dhall et al. 2002, Lau et al. 2004, Perri et al. 2005, Hosia-Randell et al. 2008, Ruggiero et al. 2009). PID use was associated with impaired physical condition (Dhall et al. 2002), cerebrovascular diseases and dependency (Vieira de Lima et. al. 2013), not having communication problems (Lau et al. 2004), and higher number of comorbidities (Landi et al. 2007, Lin et al. 2008, Ruggiero et al. 2010, Stafford et al. 2011, Cahir et al. 2014). Also mental health problems (Lau et al. 2004, Vieira de Lima et al. 2013), feeling depressed, and poor subjective health were associated with risk of receiving inappropriate medication (Pitkälä et al. 2002a).

According to a review article, female sex, lower age, being less educated, having more than one prescriber, polypharmacy, and comorbidities were predictors for receiving PIDs in institutionalized settings (Ruggiero et al. 2009).

2.2.2.4 Adverse events related to Beers' drugs

Hospitalizations and mortality

Adverse events related to Beers' drugs are summarized in Table 3.

A systematic review from all health care settings explored outcomes associated with the use of Beers' criteria PIDs (Jano and Aparasu 2007). Use of PIDs among community-living older people was associated with hospitalizations, but there was no evidence of an association with other health care use, costs, or mortality. In nursing home settings, there was no association with mortality, and the association with hospitalizations was inconclusive (Jano and Aparasu 2007). In a retrospective cohort study, the use of Beers' drugs was associated with the risk of nursing home transition (Zuckerman et al. 2006).

A few studies have suggested an association between the use of PIDs and adverse events. According to a cross-sectional study among NH residents, PID users were exposed to potential drug-drug interactions (Hosia-Randell et al. 2008). A retrospective observational cross-sectional study showed that the number of PIDs among nursing home residents was associated with pharmaceutical costs, but there was no association with mortality (Gupta et al. 1996). Conversely, by minimizing the number of potentially inappropriate medications that prescribers and pharmacies used, the total pharmaceutical costs may be decreased (Gupta et al. 1996). According to a US study, nursing home residents receiving any Beers' drug had a greater risk of being hospitalized or to be deceased than those not receiving any Beers' drug, also after multivariate analysis of longitudinal cohort data (Lau et al. 2005). In a Swedish population-based, longitudinal cohort study, community-dwelling older people (≥75 years) using PIDs according to several criteria had an increased risk of hospitalization, but not mortality. However, people living in sheltered housing or nursing homes did not show an association between the use of PIDs and hospitalization or mortality (Klarin et al. 2005). Nevertheless, this Swedish study used Beers' criteria only as part of their definition for PIDs. According to a longitudinal cohort study using Beers' 1997 criteria among NH residents, only propoxyphene was significantly associated with adverse health outcomes like hospitalizations (Perri et al. 2005). In a retrospective cohort study, the use of PIDs among home-dwelling older people was associated with drug-related problems, e.g. falling and confusion, increased costs, and increased use of health care services (Fick et al. 2008). In the US study, patients aged 65 years and over admitted to hospital had a significantly longer stay in hospital if they received at least three PIDs according to Beers' 2012 criteria (Hagstrom et al. 2015).

However, there are several other studies suggesting no association between the use of PIDs and adverse events. Potentially inappropriate drugs among Finnish older people had no effect on mortality, hospital admissions, or acute hospital stays (Raivio et al. 2006). According to a retrospective cohort study, there was no association between the use of Beers' 2003 criteria PIDs and negative health outcomes (in-hospital mortality, adverse drug reactions, or length of stay) among hospitalized older Italian people (Onder et al. 2005). Nine years later, a cross-sectional study in Italian internal medicine and geriatric ward patients aged ≥65 years was performed. Of patients, 20% and 24% were receiving Beers' criteria 2003 or 2012 drugs, respectively. After a 3-month follow-up, the use of Beers' drugs was not associated with a higher risk of adverse clinical events, rehospitalization, or all-cause mortality in univariate or multivariate analyses (Pasina et al. 2014). According to the ULISSE project in Italy, use of Beers' criteria 2003 PIDs among NH residents at baseline was associated with an increased risk of hospitalization during the following 12 months compared with residents not receiving PIDs (Ruggiero et al. 2010). The use of ≥2 Beers' 2012 PIDs among Irish community-dwelling older people (N=931) was not associated with hospitalizations, whereas the use of ≥2 STOPP criteria was (Cahir et al. 2014).

Australian nursing home residents and other people ≥65 years receiving PIDs were investigated for an association with unplanned hospital admissions (Price et al. 2014). An association was present in both groups. After adjusting for health and medication profiles, there was 20% greater risk of unplanned hospitalization in older people receiving PIDS than in their peers not receiving PIDs (Price et al. 2014). When the number of daily doses of PIDs increased in this group, the risk of unplanned hospitalization also increased. In addition, when the number of doses per day increased, the risk of hospitalization of nursing home residents increased (Price et al. 2014). This may be explained by frail older people's susceptibility to adverse effects of PIMs (Table 3).

The prevalence of emergency department (ED) visits for adverse drug events in USA has increased in 10 years from 2.4 to 4.0 per 1000 ED visits annually. Beers' criteria medications were found to be responsible for only 1.8% of ED visits for adverse drug events (Shehab et al. 2016). In a European study, Beers' 2003 criteria PIDs were considered to be responsible for 6% and STOPP criteria PIMs for 11% of hospital admissions (Gallagher and O'Mahony 2008).

According to a recent systematic review including 39 studies, most (n=33) of which used Beers' criteria, 22 articles reported an association between the use of PIDs and hospitalizations, and seven

articles reported an association of PIDs with higher costs among older adults (Hyttinen et al. 2016). PID users had also more hospitalizations than non-users, both home-dwelling older people and nursing home residents. The use of PIDs also increased the number of health care and emergency department visits (Hyttinen et al. 2016).

Quality of life

According to a population-based data with a 2-year follow-up, use of Beers' 1997 PIDs among people aged 65 years and over predicted lower self-perceived health status (Fu et al. 2004). A systematic review exploring Beers' PIDs found that the use of PIDs was associated with adverse drug reactions, but not with health-related quality of life (HRQoL) (Jano and Aparasu 2007).

Among non-institutionalized people, the use of Beers' inappropriate drugs was not associated with quality of life (QoL) (Franic and Jiang 2006). In a cross-sectional Australian study, there was no association between the use of PIDs based on Beers' 2003 criteria and QoL (Bosboom et al. 2012); the same is true of a Malaysian prospective follow-up study with STOPP criteria among nursing home residents (Al Aqqad et al. 2014). However, polypharmacy and Drug Burden Index (DBI) (exposure to anticholinergic and sedative medications) were negatively associated with QoL (Bosboom et al. 2012).

Use of PIDs may also have an effect on physical performance and function (Landi et al. 2007). Italian home-dwelling people aged 80+ years using PIDs had a lower physical battery score, walking speed, balance and chair stand test, and hand grip strength, also after adjusting for age and other potential confounders. Subjects using two inappropriate drugs had lower results in walking speed, physical performance battery score, and ADL score than those using one or none (Landi et al. 2007).

Table 3. Hospitalizations and mortality related to use of Beers' PIDs.

Study/country/setting	N/females, (mean) age years	Study design, follow-up, Beers' criteria considered	Findings
Hospitalizations, use of services, QoL, costs			
Gupta et al. 1996, USA (ICF)	19932/74%, 60% ≥81	Retrospective, cross-sectional, 1991	Number of PIDs associated with costs of pharmaceutical services
Lau et al. 2005, USA (NH)	3372/74%, 50% ≥85	Retrospective cohort, 1 year, 1991, 1997	Risk of hospitalization increased
Onder et al. 2005, Italy (H)	5152/52%, 79	Register study, 2003	No association with length of stay
Perri et al. 2005, USA (NH)	1117/82%, 85	Cohort, 5 months, 1997	PIDs associated with hospitalizations and ED visits
Klarin et al. 2005, Sweden (CD, SH, NH)	785/58%, 82	Longitudinal cohort study, 3 years, 1997	Increased risk with ≥1 hospitalization among community-dwelling persons aged ≥75 years
Raivio et al. 2006, Finland (NH+AH)	425/82%, 86	Retrospective cohort, 2 years, 2003	No association with hospital admissions, or acute hospital stays
Zuckerman et al. 2006, USA	487383, 56%, 74	Retrospective cohort, 2 years, 2003	Association with risk of nursing home transition
Lin et al. 2008 Taiwan (H)	5741/ 56%, 75	Cohort, 6 months, 2003	Risk of hospitalization increased
Fick et al. 2008, USA (HD)	16877/ 71%, 73	Retrospective cohort, 6 months, 2003	Health care utilization and costs increased among users of PIDs
Ruggiero et al. 2010, Italy (NH)	1716/72%, 84	Prospective, 1 year, 2003	Association with hospitalizations
Stockl et al. 2010, USA (CD)	37358, 75%, ≥65	Retrospective cohort, 1 year, 2003 and Zhan criteria	PID use associated with higher medical and health care costs
Bosboom et al. 2012, Australia (RAFC)	226/75%, 86	Cross-sectional, 2003	Exposure to PIDs not associated with lower QoL
Vieira de Lima et al. 2013, Brazil (LTCF)	261/58%, >60y	Cross-sectional, 2012, all categories	No association with hospitalizations
Cahir et al. 2014, Ireland (CD)	931/54%, 78	Retrospective cohort, 6 months, 2012	No association with hospitalizations
Pasina et al. 2014, Italy (H)	844, 51%, 79	Cross-sectional, 3 months, 2003, 2012	No association with re-hospitalizations
Price et al. 2014, Australia (NH, HD)	251305, N.A. ≥65	Case-time-control, register study, 2003	Use of PIDs associated with unplanned hospitalizations in both groups
Hagstrom et al. 2015, USA (H)	560/47%, 32% ≥85	Cross-sectional, 30 days, 2012	≥3 PIMs associated with length of stay and higher costs
Mortality			
Gupta et al. 1996, USA (ICF, NH)	19932/74%, 60% ≥81	Retrospective, cross-sectional, 1991	No association with mortality
Lau et al. 2005, USA (NH)	3372/74%, 50% ≥85	Retrospective cohort, 1 year, 1991, 1997	Risk of death increased
Onder et al. 2005, Italy (H)	5152/52%, 79	Register study, 2003	No association with mortality
Perri et al. 2005, USA (NH)	1117/82%, 85	Cohort, 5 months, 1997	Use of PIDs associated with mortality
Klarin et al. 2005, Sweden (CD, SH, NH)	785/58%, 82	Longitudinal cohort study, 3 years, 1997	No association with mortality
Raivio et al. 2006, Finland (NH, AH)	425/82%, 86	Retrospective cohort, 2 years, 2003	No association with mortality
Pasina et al. 2014, Italy (H)	844/ 51%, 79	Cross-sectional, 3 months, 2003, 2012	No association with mortality

AH=acute hospitals; CD = community dwelling; DBI= Drug burden index; ED =emergency department; H=hospitalized; HD=home dwelling; ICF=intermediate care facilities; LTCF= Long-term care facilities; N.A. = not applicable; NH= nursing homes; QoL= Quality of life; RAFC= Residential aged care facilities; SH =Sheltered housing

2.2.3 Drugs with anticholinergic properties (DAPs)

2.2.3.1 Cholinergic transmission

Acetylcholine is a neurotransmitter that acts on both the peripheral autonomic nervous system and the central nervous system (CNS) (Rang et al. 2016). Acetylcholine acts via muscarinic (M1-5) (Kay et al. 2005, Rang et al. 2016) and nicotinic receptors (Rang et al. 2016). Activating muscarinic receptors in the peripheral parasympathetic nervous system causes effects such as heart rate decrease, urinary bladder contraction, urinary sphincter relaxation, salivary gland blood vessel dilatation, salivary gland secretion, eye pupil constriction, and ciliary muscle contraction (Karimi et al. 2012, Rang et al. 2016). The location and effect of blockage of different five receptors are presented in Table 4. The brain also has nicotinic receptors, which act via other mediators like glutamate and dopamine (Rang et al. 2016). However, the term 'anticholinergic' traditionally refers to muscarinic receptor antagonism (Gerretsen and Pollock 2011).

Table 4. Muscarinic receptors (M 1-5) in the central nervous system (CNS) and other tissues (Kay et al. 2005, Karimi et al. 2012).

Subtype	General distribution in the CNS	Non-CNS locations	Effect of blockage of receptor
M_1	In cerebral cortex, hippocampus, and neostriatum (constitute about half of total acetylcholine receptors in CNS)	Salivary glands, sympathetic ganglia	Impairment of cognitive function, delirium, dry mouth
M_2	Located throughout CNS	Smooth and cardiac muscle, detrusor muscle of the bladder	Cognitive decline, delirium, constipation, urinary retention
M_3	Low levels throughout CNS	Smooth muscle, salivary glands, eyes, detrusor muscle of the bladder	Dry mouth, constipation, urinary retention, blurred vision
M_4	In neostriatum, cortex, and hippocampus	Salivary glands	Impairment of cognitive function, delirium, dry mouth
M_5	Projection neurons of substantia nigra pars compacta and ventral tegmental area, and hippocampus	Eyes (ciliary muscle)	Blurred vision

Drugs with anticholinergic properties (DAPs) are able to block cholinergic muscarinic receptors. Some DAPs are used specifically for this effect like drugs to treat an overactive bladder, muscle spasms, chronic obstructive pulmonary disease (COPD), and Parkinson's disease. However, DAPs also have a number of unwanted effects (Kay et al. 2005, Lechevallier-Michel et al. 2005, Uusvaara et al. 2011, Salahudeen et al. 2014, Nishtala et al. 2016). Because of the increased permeability of the blood-brain barrier and age-related pharmacodynamic changes, the ageing brain is particularly sensitive to adverse effects of DAPs (Ehrt et al. 2010). Many commonly used drugs are prescribed for older people without recognition of the anticholinergic properties of these medications (Nishtala et al. 2016).

2.2.3.2 Definitions of DAPs

Cumulative exposure to multiple medicines with anticholinergic properties is known as anticholinergic burden (Tune 2001). A number of scales have been developed to define drugs with anticholinergic properties and to measure the anticholinergic burden (Han et al. 2001, Ancelin et al. 2006, Carnahan et al. 2006, Hilmer et al. 2007, Boustani et al. 2008, Chew et al. 2008, Han et al. 2008, Rudolph et al. 2008, Ehrt et al. 2010, Sittironnarit et al. 2011) (see Table 5). Some authors have graded the levels of anticholinergic effect for various drugs, and anticholinergic burden can be measured by summing up the number of drugs and/or their level of effect on the person using them (e.g. Carnahan et al. 2006, Rudolph et al. 2008). Drug burden index (DBI) takes into account both DAPs, sedative drugs, and total number of medications (Hilmer et al. 2007). DBI is calculated using a formula developed for this purpose. Anticholinergic burden has also been measured using serum anticholinergic activity (SAA) (Chew et al. 2008). However, there is no consensus which definition or which standardized method should be used. Only a few studies have compared how various criteria identify the burden of DAPs and how these DAPs according to the different criteria overlap. Researchers have found low concordance between Anticholinergic Drug Scale (ADS) (Carnahan et al. 2006), Anticholinergic Risk Scale (ARS) (Rudolph et al. 2008), and Anticholinergic Cognitive Burden (ACB) (Boustani et al. 2008, Lertxundi et al. 2013, Naples et al. 2015).

Table 5 provides examples of various criteria to define DAPs. In most of the criteria, the anticholinergic effect has been graded with a scale in which low points indicate lower levels of anticholinergic activity and higher points higher activity. Most lists are based on expert opinion and/or literature review, previous anticholinergic lists, or SAA measures. The number of anticholinergic drugs varies between 27 to 195 according to different definitions and scales.

Various lists of DAPs and DAP scales have shown associations of DAPs with adverse effects, thus, prognostic validity. For example, the use of drugs according to Carnahan's Anticholinergic Drug Scale (ADS), Rudolph's Anticholinergic Risk Scale (ARS), or Chew's list showed associations with poor vision, cognitive decline, and depression (Lampela et al. 2013). Many anticholinergic lists have been associated with poorer cognitive function (Ancelin et al. 2006, Hilmer et al. 2007, Boustani et al. 2008, Han et al. 2008, Uusvaara et al. 2009, Ehrt et al. 2010, Sittironnarit et al. 2011). However, none of these methods have been widely accepted to assess anticholinergic burden in clinical practice.

Table 5. Criteria for defining drugs with anticholinergic properties.

Reference	Criteria	Grading system	Based on	No. of DAPs	Comments
Ancelin et al. 2006, France	Anticholinergic Burden Classification (ABC)	4-point, 0 to 3 point scale	SAA and expert opinion	27	Use of DAPS associated with mild cognitive impairment
Carnahan et al. 2006, USA	Anticholinergic Drug Scale (ADS)	4-point, 0 to 3 point scale	Expert opinion	117	Total dose-adjusted ADS scores were associated with SAA
Hilmer et al. 2007, USA	Drug Burden Index (DBI)		Calculates cumulative exposure to both anticholinergic and sedative medications based on a dose response-derived formula		Associated with poorer physical and cognitive performance among well-functioning older people
Boustani et al. 2008, USA	Anticholinergic Cognitive Burden Scale (ACB)	4-point, 0 to 3 scale	Literature review, expert opinion	88	Relationship between different DAPs and negative effects on cognition
Chew et al. 2008, USA	Chew's list, based on Serum Anticholinergic Activity (SAA)	5-point, 0 to 4 scale	SAA measure using radioreceptor assay, 107 medications most frequently used by older LTC residents	39	SAA measures anticholinergic activity in vitro
Han et al. 2001, Han et al. 2008, USA	Clinician-rated Anticholinergic Score (CrAS)	4-point, 0 to 3 point scale	Previous published anticholinergic scale and expert opinion	60	Increase in delirium symptom severity in older people with delirium, cumulative anticholinergic exposure affected negatively verbal memory and executive function in older men
Rudolph et al. 2008, USA	Anticholinergic Risk Scale (ARS)	4-point, 0 to 3 scale	Literature review and expert opinion	49	ARS score associated with the risk of central and peripheral adverse effects Drugs are listed in Appendix 3
Uusvaara et al. 2009, Finland	Drugs with Anticholinergic Properties	3-point, 0 to 2	Previous anticholinergic scales	30	Higher number of DAPS is related to lower cognition
Ehrt et al. 2010, Norway	Anticholinergic Activity Scale (AAS)	5-point, 0 to 4 scale	Chew et al. 2008, literature review, expert opinion	29	Association between use of DAPs and cognitive decline in Parkinson's disease
Socialstyrelsen 2010, Socialstyrelsen 2017, Sweden	Svenska Socialstyrelsen's list	2-point, 0 to 1 scale	Literature review, expert opinion	31	National Board of Health and Welfare of Sweden. Drugs 2010 are listed in Appendix 3
Sittironnarit et al. 2011, Australia	AntiCholinergic Load (ACL)	3-point, 0 to 2 scale	Previous anticholinergic scales (SAA, ARS, CrAS, ABC), expert opinion	49	Modest negative effects on psychomotor speed and executive function in HC, no effect in MCI and AD
Durán et al. 2013, Ecuador	Review, Duran's list, summary of seven different lists	3-point, 0 to 2 scale	Previous anticholinergic scales (ADS, ABC, SAA, ARS, CrAS, AAS, and ACL)	100	More knowledge needed about dosing and route of administration

AD= Alzheimer's disease; HC=healthy controls; MCI= mild cognitive impairment

Serum anticholinergic activity (SAA) has been considered important in quantifying anticholinergic burden; it measures anticholinergic medications, metabolites, and possibly endogenous substances (Chew et al. 2008). Evidence suggests an association between higher SAA and lower cognition in a small sample (Chew et al. 2005). However, if SAA is determined to be elevated, this does not provide any guidance as to which medications should be discontinued (Carnahan et al. 2006). When SAA from 107 most frequently used medications by older long-term care (LTC) residents was measured, 39 showed detectable SAA (Chew et al. 2008). Measurement of SAA is not widely available clinically (Gerretsen and Pollock 2011). In addition, it is a measure of anticholinergic activity in serum, not in CNS (Gerretsen and Pollock 2011). Besides, it has been argued that this value is no better than lists of drugs with known anticholinergic properties (Lampela et al. 2013). A cross-sectional Finnish study found no association between SAA levels and cognition or other anticholinergic adverse drug events (Lampela et al. 2013). According to a recent systematic review and meta-analysis, four studies showed no association between SAA and cognitive decline, whereas four studies supported this association. In conclusion, SAA has limitations and its use is still under development (Salahudeen et al. 2016).

2.2.3.3 Prevalence of DAPs in institutional settings

The prevalence of the use of DAPs has varied according to the definition used, population characteristics, and time when study performed (Uusvaara et al. 2011, Salahudeen et al. 2015). Many definitions include older drugs, which are no longer used, affecting prevalence rates. In addition, different countries have various DAPs available. When anticholinergic medication was calculated by using nine different scales, prevalence of DAPs varied widely, from 23% to 56%, among the same participants (Salahudeen et al. 2015).

In institutional settings, the prevalence rates for DAPs have varied between 12% and 82% (Table 6). Some studies include only drugs with high anticholinergic burden, thus providing fairly low prevalence rates (Kersten et al. 2013b). Use of Socialstyrelsen's list has yielded fairly low prevalences (12-21%), which may reflect the low number of drugs included in the list or the good quality of prescribing in Sweden (Bergman et al. 2007, Olsson et al. 2010, Haasum et al. 2012). One Italian study and two Finnish studies used the same ARS score (Rudolph et al. 2008) and showed fairly similar prevalences (42-55%) in long-term care settings (Kumpula et al. 2011, Teramura-Grönblad et al. 2011, Landi et al. 2014). The highest prevalence was found in USA (74-82%) in studies using either ACB score (Boustani et al. 2008) (Kolanowski et al. 2009, Palmer et al.

2015) or ADS scale (Carnahan et al. 2006) (Chatterjee et al. 2010), both of which include a high number of DAPs.

2.2.3.4 Factors associated with use of DAPs

According to a large Swedish register-based study, the use of DAPs was associated with living in an institution (OR 2.58, 95% CI 2.48 to 2.68) (Haasum et al. 2012). According to a study among nursing home (NH) residents with dementia, higher age, impaired decision-making ability, and behavioural symptoms were negatively associated with the use of DAPs according to ADS level 2-3, whereas higher number of drugs, schizophrenia, depression, anxiety, and Parkinson's disease were positively associated with administration of these moderate and strong DAPs (Chatterjee et al. 2010). According to a Finnish cross-sectional study in residential care facilities, lower age, higher number of drugs, use of cholinesterase inhibitors, psychiatric disorders, Parkinson's disease, and higher level of disability were associated with the use of DAPs (Teramura-Grönblad et al. 2011). According to a population-based prospective cohort study, DAP users were more likely to be women, to have poor self-rated health, to have higher levels of depressive symptoms, and to have higher comorbidity than non-users (Gray et al. 2015).

Among Finnish 400 community-dwelling older people (75-90 years) with cardiovascular diseases, 74% used one or more DAPs (Uusvaara et al. 2011). Uusvaara defined DAPs by his own criteria, including 30 drugs based on the literature (Uusvaara et al. 2011). In a longitudinal study with both home-dwelling and institutionalized people, 47% used drugs with possible anticholinergic properties (Fox et al. 2011). Associating factors were older age, lower social class, former smoking, and more health conditions (Fox et al. 2011). In a Finnish national population cohort study, 51% of community-dwelling individuals with Alzheimer's disease (AD) aged ≥65 years had been exposed to DBI medications (Gnjidic et al. 2014). DBI includes sedative drugs in addition to DAPs (Hilmer et al. 2007). Of people with AD, 16% had a high DBI; the respective figure was 8.7% among people without AD (Gnjidic et al. 2014). According to an Italian study, cognitive impairment and younger age were associated with DAP use in NHs (Landi et al. 2014). Of 235 home-dwelling Parkinson's disease patients, 43% used DAPs and the use was associated with lower education and lower MMSE score and higher depressive and motor symptoms (Ehrt et al. 2010).

Table 6. Prevalence of DAPs in institutional settings.

Study, country (setting)	N/ Females %	Age, years	Study design, criteria	Prevalence, %	Comments
Bergman et al. 2007, Sweden (NH)	7904/70%	85	Cross-sectional register, Swedish quality indicators list	20	Higher number of prescribers associated with lower quality of drug therapy
Kolanowski et al. 2009, USA (NHD)	87/77%	86	Cross-sectional, ACBS	82	56% received at least 2 DAPS, 37% at least 1 strong DAP
Nurminen et al. 2009, Finland (LTCW)	154/73%	84	Cross-sectional, Beers' 2003 and Socialstyrelsen 2003	17	Study explored chemical restraints and related strong anticholinergics use
Chatterjee et al. 2010, USA (NHD)	692653/77%	57% ≥85	Cross-sectional, register, ADS score	74 any, 21 strong	
Olsson et al. 2010, Sweden (NH, SCUD)	3705/72	85	Cross-sectional, Swedish quality indicators list	NH 21 NHD 19	Negative correlation between quality of prescribing and number of prescribers
Kumpula et al. 2011, Finland (LTCH)	1004/75%	81	Prospective cohort, one year all-cause mortality, ARS score	55 any, 36 mild, 19 strong	Higher anticholinergic scores were not associated with mortality
Teramura-Grönblad et al. 2011, Finland (RCF)	1475/78%	82-84	Cross-sectional, ARS score	42	RCFs provide care similar to NHs. Use of DAPs associated with lower PWB
Luukkanen et al. 2011, Finland (AGW, NH)	425/82%	86	Cross-sectional, literature	80 ≥2	In logistic regression analysis, no association with delirium or 2-year mortality
Haasum et al. 2012, Sweden (IR)	86721/70%	86	Cross-sectional retrospective, Swedish quality indicators list	12	Use of antidementia drugs was negatively associated with use of DAPs, institutionalism was positively associated with the use of DAPs
Kersten et al. 2013b, Norway (NH)	1101/N.A.	Median 87 (participants)	Cross-sectional, ADS score ≥3	21% had ADS score ≥3	87 participants in study, no gradual decline in cognitive function when ADS score increased above 3
Landi et al. 2014, Italy (NH)	1490/72%	Median 84	Observational, multicentre, prospective 1-year cohort, ARS	48	Use of DAPs associated with falls, functional decline, and delirium
Palmer et al. 2015, USA (NHD)	69877/79%	84	Cross-sectional cohort, ACBS	77 any, 67 ACBS level 1, 3 level 2 and 31 level 3	13% used concomitantly ABS scale levels 2 or 3 and AChEIs

ACBS=Anticholinergic Cognitive Burden Scale (Boustani et al. 2008); AChEI=Acetyl-CholinEsterase-Inhibitor, ADS=Anticholinergic Drug Scale (Carnahan et al. 2006); AGW=acute geriatric ward; ARS= Anticholinergic Risk Scale (Rudolph et al. 2008); DAPs=Drugs with Anticholinergic Property; IR=institutionalized residents; LTCH=long-term care hospitals; LTCW=Long.Term Care Wards; N.A.= not applicable; NH=nursing homes; NHD=nursing homes for dementia; PWB=Psychological Well-Being; QoL=Quality of Life; RCF=Residential Care Facilities; SCUD=special care units for dementia

2.2.3.5 Adverse events related to DAPs

Drugs with anticholinergic properties are known to be associated with a number of adverse drug reactions such as central nervous system effects, e.g. cognitive impairment, delirium, and falls, and peripheral side effects, e.g. dry mouth, dry eyes, mydriasis, anhidrosis, constipation, and urinary retention (Tune 2001, Rudolph et al. 2008, Puustinen et al. 2011, Gerretsen and Pollock 2011, Puustinen et al. 2012, Nishtala et al. 2016). The cholinergic neuron system is damaged in patients with dementia, and therefore, anticholinergic medication may lead to worsening of cognitive impairment (Chatterjee et al. 2010, Lechevallier-Michel et al. 2005) and may even be a risk factor for psychosis (Cancelli et al. 2008).

Adverse effects related to the use of DAPs are well-known peripheral effects, such as dry mouth, tachycardia, urinary retention, constipation, peristaltic reduction, and inability to accommodate vision, and central effects, such as cognitive impairment, behavioural excitation, attention deficits, and delirium (Tune 2001, Boustani et al. 2008, Karimi et al. 2012, Salahudeen et al. 2014). Dry mouth may lead to increased risk of respiratory infections, dental problems, impaired nutritional status, and communication problems (Tune 2001). Constipation may cause pain, lead to increased use of laxatives, and urinary retention may cause discomfort and predispose to urinary tract infections and need for catheterization (Tune 2001). According to a review article, among individuals 80 years and older, increased exposure to DAPs was associated with negative health outcomes such as cognitive and physical impairment and falls. However, the relationship with hospitalization and mortality remained inconclusive (Cardwell et al. 2015). Use of DAPs seemed to be associated with lower physical function (Lowry et al. 2011, Landi et al. 2014).

Thus, DAPs may have a number of unpleasant side effects and they may have a negative impact on the quality of life. In one study, anticholinergic burden did not have a relationship with the quality of life indicator “engagement in activities” (Kolanowski et al. 2009). However, in a Finnish study, the use of DAPs was associated with poor psychological well-being (Teramura-Grönblad et al. 2011).

Hospitalizations and falls

In a population-based study consisting of 537 387 people, nine different anticholinergic risk scales and associations of adverse health outcomes were compared (Salahudeen et al. 2015). Anticholinergic burden scores irrespective of the anticholinergic scale were independently

associated with a greater risk of hospital admissions, fall-related hospitalizations, hospital length of stay, and more visits to general practitioners (Salahudeen et al. 2015).

According to a Finnish prospective study among community-dwelling older people with a mean follow-up of 3.3 years, there was an association between the use of DAPS and an increased number of hospital days (Uusvaara et al. 2011). In a Finnish cohort study with a follow-up of over one year, a dose-response relationship was found between cumulative anticholinergic and sedative drug use and hospitalizations in community-dwelling people with and without dementia (Gnjidic et al. 2014). According to a prospective multicentre observational study data, the use of DAPs was associated with negative outcomes such as falls, functional decline, and delirium (Landi et al. 2014).

According to an Australian study with a 12-month follow-up, there was an association between DBI and falls among older people living in residential aged care facilities (RACFs) (Wilson et al. 2011). IRR was 1.69 (95% CI 1.22 to 2.34) for low DBI (<1) and 2.11 (95% CI 1.47 to 3.04) for high DBI (≥1) compared with those with DBI of 0 (Wilson et al. 2011). According to a cohort study among people 65 years and older, the use of DAPs was associated with central adverse effects like falls (Rudolph et al. 2008). A multicentre study found that exposure to DAPs and sedative drugs increased the risk for in-hospital falls (Dauphinot et al. 2014). According to a review article, the use of DAPs may be associated with reduced physical function, and avoiding DAPs may preserve function and prevent falls (Fox et al. 2014).

In an Australian retrospective cohort study with a 2-year follow-up, DAPs were defined by anticholinergic risk scale (ARS) (Rudolph et al. 2008) and anticholinergic drug scale (ADS) (Carnahan et al. 2006) (Kalisch Ellett et al. 2014). Individuals taking at least two DAPs had IRR 2.58 (95% CI 1.91 to 3.48) and those taking three or more DAPs IRR 3.87 (95% CI 1.83 to 8.21) for hospitalization for confusion or dementia (Kalisch Ellett et al. 2014).

Mortality

In a Finnish retrospective study among operated male hip fracture patients with a 3-year follow-up, the use of potent anticholinergic drugs was associated with increased mortality (Panula et al. 2009). However, two other Finnish studies found no association between anticholinergic drug use and mortality (Kumpula et al. 2011, Uusvaara et al. 2011). According to a Finnish cohort study with a 2-year follow-up, there was no association between the use of DAPs and delirium or 2-year mortality (Luukkanen et al. 2011). However, Gnjidic and colleagues (2014) reported a dose-response relationship between cumulative anticholinergic and sedative drug use and mortality.

Based on a secondary analysis of an Australian educational RCT aiming to improve patient-based outcomes among patients in palliative care, there was no association between anticholinergic load and mortality (Agar et al. 2010). This RCT used a modified Clinician-Rated Anticholinergic Scale (Han et al. 2001, Han et al. 2008). In another Australian study in residential aged care facilities, no significant association was present between increasing DBI score and all-cause mortality (Wilson et al. 2012). According to a large prospective longitudinal study using the ACB scale (Boustani et al. 2008) to define DAPs, the use of drugs with possible and definite anticholinergic properties was associated with increased mortality during a 2-year follow-up (Fox et al. 2011). Among older hospitalized patients, higher ARS scores (Rudolph et al. 2008) with, but not without, hyponatremia predicted mortality (Lowry et al. 2011). Increased exposure to anticholinergic and sedative medications was not associated with mortality in a multicentre cohort study (Dauphinot et al. 2014). The EPIC-Norfolk prospective study found an association between the use of DAPs and mortality. Participants were aged from 40 to 79 years (Myint et al. 2015).

According to a systematic review article examining nine studies, there was no clear evidence for an association between use of DAPs and increased mortality (Fox et al. 2014).

Ruxton with researcher colleagues (2015) investigated associations between the use of DAPs and all-cause mortality, falls, and cognitive impairment in a systematic review and meta-analysis. Associations emerged between the use of DAPs and mortality according to drug class, individual medications, and drug scoring systems. In the meta-analysis, the ACB scale showed a significant association with all-cause mortality (OR 2.06, 95% CI 1.82 to 2.33).

DAPs and cognition

A relationship exists between cognition and acetylcholine function in the brain. In young people, scopolamine injection induced cognitive deficits more similar to that occurring in non-demented older people than to that found in Alzheimer's disease (Flicker et al. 1990). Blockade of cholinergic transmission might lead to the development of both acute and chronic cognitive impairment (Boustani et al. 2008). Older people are particularly vulnerable to cognitive impairment resulting from DAP use. They have changes in blood-brain barrier ultrastructure and permeability, reduction in density of muscarinic receptors in the brain, high comorbidity, and polypharmacy, which often lead to accumulation of DAPs (Kay et al. 2005). The increase in blood-brain barrier permeability may allow DAPs to cross the blood-brain barrier, resulting in increased sensitivity to the central nervous adverse effects of DAPs (Karimi et al. 2012).

Drugs with properties to inhibit acetylcholinesterase, the enzyme that hydrolyses acetylcholine, are used in the treatment of Alzheimer's disease (AD), and they have the potential to slow the decline in cognition (Ellis 2005). According to a systematic review and meta-analysis, acetylcholinesterase inhibitors (AChEIs) have only a limited effect in treatment of AD, but there is a lack of other effective medications for AD (Hansen et al. 2007). When DAPs are used concomitantly with AChEIs, DAPs may reduce the effect of AD medication (Lu and Tune 2003). Despite this, concomitant use of AChEIs and DAPs is common (Kolanowski et al. 2009, Modi et al. 2009, Teramura-Grönblad et al. 2011, Bell et al. 2012, Palmer et al. 2015). According to a register-based Swedish study, the use of DAPs was more common among cholinesterase inhibitor users than non-users (Johnell and Fastbom 2008). In USA, nearly half of nursing home residents with dementia taking cholinesterase inhibitors were concomitantly using DAPs (Modi et al. 2009). DAPs were often used to treat adverse effects of acetylcholinesterase inhibitors such as urinary incontinence and gastrointestinal upset (Modi et al. 2009, Bell et al. 2012).

Cognitive performance among 1780 home-dwelling subjects aged 70 years or over was studied in a French cohort study (Lechevallier-Michel et al. 2005). In multivariate logistic regression models, the use of DAPs showed a trend to produce worse results in the MMSE ($p=0.05$), but was significantly associated with lower visual memory ($p=0.015$) and lower verbal fluency ($p=0.0015$) (Lechevallier-Michel et al. 2005). DAPs may also be associated with mild cognitive impairment. According to a longitudinal cohort study, people aged over 60 years with a one-year consistent exposure to DAPs were significantly more often classified as mildly cognitively impaired than non-users (Ancelin et al. 2006). However, there was no difference between users and non-users in the risk of developing dementia at follow-up after eight years (Ancelin et al. 2006).

DAPs contribute to cognitive impairment, confusion, and delirium (Han et al. 2001, Rudolph et al. 2008, Campbell et al. 2009, Cancelli et al. 2009). According to a prospective cohort study with a 2-year follow-up, cumulative anticholinergic exposure may negatively affect verbal memory and executive function in older men (Han et al. 2008).

According to a Finnish cross-sectional study, there was an inverse association between the number of DAPs and Mini-Mental State Examination (MMSE) scores, the lowest MMSE scores obtained by subjects with apolipoprotein E4-allele (APOE4), also after adjustments (Uusvaara et al. 2009). The results were similar when Clinical Dementia Rating Scale (CDR) scores were used to reflect cognitive function (Uusvaara et al. 2009). When these same participants were divided into two

groups, those using one or more DAPs and those not using DAPs, a higher proportion of users had low verbal fluency (<16) and low naming test (<12/15) in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery relative to non-users, also after adjusting for age, sex, and education (Uusvaara et al. 2013). According to a longitudinal cohort study, there was significant association between ApoE4 allele and sensitivity to DAP use. Those women with ApoE4 allele taking DAPs had a 2-fold higher risk of global cognitive decline than women without ApoE4 allele taking DAPs (Carrière et al. 2009).

Cancelli et al. (2008) found in a cross-sectional study containing 230 AD patients an association between the use of DAPs and psychosis (OR 2.52, 95% CI 1.27 to 5.00). Fox et al. (2011) used the ACB scale to define DAPs in a prospective longitudinal study with a 2-year follow-up. After adjustment, the use of drugs with definite anticholinergic properties was associated with a greater decline in cognition compared to non-use; the same was not true for drugs with possible anticholinergic properties. In a longitudinal cohort study with an 8-year follow-up, an association was present between the use of DAPs and the rate of cognitive decline among patients with Parkinson's disease (Ehrt et al. 2010). A Finnish longitudinal population-based study found an association between anticholinergic use and decline in cognitive functioning only in men (Puustinen et al. 2011).

In a randomized controlled trial training to reduce DAP use in nursing homes, ADS score (Carnahan et al. 2006) declined in the intervention group compared with the control group, whereas there was no improvement in cognition (Kersten et al. 2013a). However, according to a longitudinal cohort study among community-dwelling people aged 65 years or more, the risk of incident dementia was increased in those continuing DAP use (hazard ratio (HR) 1.65, 95% CI 1.00 to 2.73), but not in those discontinuing DAP use (HR 1.28, 95% CI 0.59 to 2.76) (Carrière et al. 2009). In a cross-sectional study, there was no gradual decline in cognitive function among nursing home residents when the anticholinergic scale increased above 3. However, mouth dryness worsened and serum anticholinergic activity increased (Kersten et al. 2013b). The impact of anticholinergic discontinuation on cognitive functions is poorly researched and poorly understood (Salahudeen et al. 2014).

According to a population-based prospective cohort study, higher cumulative use of anticholinergic drugs was associated with an increased risk for all-cause dementia and AD (Gray et al. 2015). In a recent study, the associations between DAP use and cognition, brain metabolism, and brain atrophy were investigated in cognitively normal adults (Risacher et al. 2016). Anticholinergic burden scale

was calculated using the ACB scale (Boustani et al. 2008). DAP use was defined as a minimum use of a drug for at least 1 month before baseline. Cognitively normal older adults predisposed to medium or high anticholinergic activity had poorer cognition, reduced cerebral glucose metabolism, increased brain atrophy, and increased clinical decline compared with non-users (Risacher et al. 2016).

A clinical review investigating the association between anticholinergic burden and cognitive side effects included 27 studies (Campbell et al. 2009). All but two studies found an association between the anticholinergic activity of medication and either cognitive impairment, dementia, or delirium (Campbell et al. 2009). According to another review, an association was noted between the use of DAPs and cognitive impairment and onset of psychotic symptoms particularly among older people with dementia and delirium (Cancelli et al. 2009). In a systematic review including nearly 61 000 participants, 77% of studies reported cognitive decline with increasing anticholinergic load, but only limited evidence about delirium (Fox et al. 2014). Furthermore, a systematic review and meta-analysis found an association between the use of DAPs and cognitive impairment (Ruxton et al. 2015) (see Table 7).

Table 7. Use of DAPs and cognitive decline.

Study, country (setting)	N/ Females %	Age, years	Study design, criteria	Results
Flicker et al. 1990, USA (CD)	30/N.A.	18 to 30	Experimental design, scopolamine	Scopolamine injection caused cognitive effects similar to normal ageing
Lu and Tune 2003, USA (CD)	69 AD patients: 53 no DAPs + 16 with DAPs/ No DAPs 49%; with DAPs 63%	No DAPs: 76 + with DAPs: 77	Retrospective cohort study, 2-year follow-up, Tune and Egeli 1999	Patients receiving donepezil+DAP(s) had significantly lower MMSE scores after follow-up
Lechevallier-Michel et al. 2005, France (CD)	1780: 244 with DAPs /58%	Median 77	Cross-sectional study (PAQUID cohort), own list including 7 drug classes	Use of DAPs was significantly associated with lower visual memory, lower verbal fluency, lower MMSE
Ancelin et al. 2006, France (CD + institutionalized)	372: 51 with DAPs/ ≈76%	> 60	Longitudinal cohort study, 1-year follow-up, combined SAA+own list	Persistent DAP users had increased risk of being classified as MCI, not of developing dementia
Han et al. 2008, USA (CD)	544: 342 with DAPs/0%	Mean age 74	Prospective cohort study, 12-month follow-up, CrAS	Cumulative DAP exposure negatively affected verbal memory and executive function
Uusvaara et al. 2009, Finland (CD)	400: 276 with DAPs/65%	Mean age 80	Cross-sectional study, list according to previous literature	Higher number of DAPs was associated with lower MMSE. APOE4 carriers vulnerable to DAPs
Carrière et al. 2009, France (CD)	6912: 520 with DAPs/60%	65+	Cohort, 4-year follow-up, combination of 3 lists	Use of DAPs was associated with increased risk of cognitive decline and dementia
Ehrt et al. 2010, Norway (CD)	235: 99 with DAPs /52%	Mean age 75	Cohort study, 8-year follow-up, AAS	Use of DAPs was associated with higher rate of cognitive decline in men with PD
Fox et al. 2011, GB (CD and institutionalized)	13004: 6010 with DAPs/60%	Mean age 75	Cohort study, 2-year follow-up, ACB	Dose-response relationship between greater ACB score and lower MMSE
Puustinen et al. 2011, Finland (CD and institutionalized)	1196/59%	Mean age 71	Longitudinal population based, mean follow-up 7.6 years	DAP use was associated with cognitive decline in men
Uusvaara et al. 2013, Finland (CD)	400: 295 with DAPs/65%	Mean age 80	Cross-sectional cohort study, list according to previous literature	DAP use associated with low naming and verbal fluency scores
Gray et al. 2015, USA (CD)	3434: 2689 with DAPs at any time point during follow-up /60%	74 median at study entry	Prospective population-based cohort study, 10-year follow-up, Beers' 2012	10-year higher cumulative exposure to DAPs was associated with increased risk of dementia
Risacher et al. 2016, USA (CD)	402: 52 with DAPs/53%	Mean age 73	Cohort, ACB scale, and other reports	Cognitively normal DAP users lower scores in several cognitive tests + reduce glucose metabolish in FDG + increased brain atrophy in MRI

AAS=Anticholinergic Activity Scale (modified Chew list (2010)); ACB=Anticholinergic Cognitive Burden Scale (Boustani et al. 2008); AD=Alzheimer's Disease; CD=Community Dwelling; CrAS=Clinician-rated Anticholinergic Score (Han et al. 2001); FDG=fluorodeoxyglucose F18 positron emission tomography; MCI=Mild Cognitive Impairment; PAQUID = Personnees Agees QUID; PD=Parkinson's Disease

2.2.4 Psychotropic drugs

Psychotropic drugs and other centrally acting drugs are in commonly use among older people (Gruber-Baldini et al. 2004, Hosia-Randell and Pitkälä 2005, Nurminen et al. 2009, Olsson et al. 2010, Lustenberger et al. 2011, Stafford et al. 2011, Bourgeois et al. 2012, Pitkälä et al. 2015). Although they are often needed to alleviate symptoms of pain, mood, Parkinson's disease, psychosis, anxiety, or dementia, they also have potential adverse effects that predispose older people to sedation and risks of cognitive decline, delirium, falls, and catastrophic disabilities (Leipzig et al. 1999, Schneider et al. 2005, Franco and Messinger-Rapport 2006, Hartikainen et al. 2007, Bloch et al. 2011, Puustinen et al. 2012, Seitz et al. 2013).

2.2.4.1 Definitions of psychotropic drugs

The Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO) classifies drugs into different categories according to their therapeutic, pharmacological, and chemical properties and the organ or system on which they act (WHO 2012). ATC central nervous system drugs (code N) include anesthetics (N01), analgesics (N02), antiepileptics (N03), antiparkinson drugs (N04), psycholeptics (N05), psychoanaleptics (N06), and other nervous system drugs (N07). Common drugs used by older people affecting the central nervous system in these categories include opioids (N02A), antiepileptics (N03A), antiparkinson drugs (N04), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D) (WHO 2012).

All of these drugs affect the central nervous system. Some of them have sedating effects as either the primary effect of the drug or an adverse effect (e.g. opioids, antiepileptics, some antiparkinson drugs, antipsychotics, anxiolytics, hypnotics, sedatives, and some antidepressants), whereas others have been designed to have other effects on the central nervous system. However, the WHO ATC code category N does not include all sedative drugs such as many anticholinergic drugs (e.g. muscle relaxants and antiemetics) (WHO 2012). Some researchers have defined drugs having a sedative load, including most WHO ATC central nervous system drugs, but also muscle relaxants, theophylline, and scopolamine (Taipale et al. 2009). This is a practical way of measuring sedative load in older people, thus, implicating potentially harmful effects on dizziness, falls, and sedation (Taipale et al. 2009). There are also other ways of defining drugs with sedative properties (Linjakumpu et al. 2003). Linjakumpu's own definition includes, besides the sedatives mentioned

above, some antitussives, proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs (NSAIDs), beta-blockers, and other cardiovascular drugs.

Most researchers have explored psychotropic medications, which have been defined solely to include antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), and sedative-hypnotics (N05C) (Hosia-Randell and Pitkälä 2005, Gobert et al. 2005, Hanlon 2010a, Wastesson et al. 2014), and sedative antihistamines have also been taken into account (Ruths et al. 2013). These drugs are commonly used in institutional settings to manage neuropsychiatric symptoms in dementia (Pitkälä et al. 2004a, Nurminen et al. 2009). The Swedish Socialstyrelsen has defined a quality indicator for inappropriate use of psychotropic drugs (Socialstyrelsen 2010, Socialstyrelsen 2017). It states that older people should never use more than two psychotropic drugs simultaneously (Socialstyrelsen 2010, Socialstyrelsen 2017). The majority of criteria for inappropriate drugs for older people include most psychotropic drugs, especially antipsychotics, anxiolytics, and long-term use of hypnotics (Laroche et al. 2007, Rognstad et al. 2009, Socialstyrelsen 2010, AGS 2012, AGS 2015, Nyborg et al. 2015, O'Mahony et al. 2015). Heterogeneous definitions reduce comparability between studies.

2.2.4.2 Prevalence of psychotropic drugs in institutional settings

The known adverse effects of psychotropic drugs are emphasized in older people (Hanlon et al. 1998, Nurminen et al. 2010, Puustinen et al. 2011, Maust et al. 2015, Aparasu et al. 2012). Despite this fact, the use of psychotropic medication is common among both home-dwelling and institutionalized older people. There have been concerns about the abundant use of psychotropic drugs among older people. The Omnibus Budget Reconciliation Act of 1987 (OBRA 87) was created to improve quality of care in US nursing homes (Omnibus Budget Reconciliation Act of 1987). It included instructions to reduce the use of psychotropic drugs. Antipsychotic drug use in US nursing homes declined after implementation of this regulation, but anxiolytics and antidepressants use remained at the same level. Use of any psychotropic drug decreased from 41% to 36% (Garrard et al. 1995). However, since 1996 use of especially antidepressants but also antipsychotics, anxiolytics and sedatives has significantly increased in American nursing homes (Hanlon et al. 2010a). Excessive psychotropic drug use among people with dementia has also received attention in France (Haute Autorité de santé AMI-Alzheimer program 2012). Contemporary use of psychotropics is common. In Sweden, 39% Of nursing home residents received three or more psychotropic drugs (Bergman et al. 2007).

According to a Swedish register-based study, about 37% of older people (75+ years) dispensed any drug used at least one psychotropic drug (Wastesson et al. 2014). According to a Finnish register-based study, 53% of community-dwelling people with AD used at least one psychotropic one year after diagnoses, the respective figure among people without AD being 33% (Taipale et al. 2014). In Finland, about 37% of community-dwelling population samples (75+ years) were on psychotropics in Lieto and Kuopio in the 1990s (Linjakumpu et al. 2002, Hartikainen et al. 2003). In Europe, 43% of home care older people were on psychotropics (Fialová et al. 2005). About 6% of home care patients in nine European countries were on antipsychotics (Alanen 2007). There was wide variation in the use of one or more antipsychotics between different countries, ranging from 3% in Denmark to 12% in Finland (Alanen 2007). Older people living in institutional settings are usually administered a higher number of psychotropic drugs than the community-dwelling elderly (Haasum et al. 2012). Whereas in 2008 3% of community-dwelling older people used >2 psychotropic drugs defined as inappropriate by Socialstyrelsen, the respective figure for institutionalized older residents was 19% (Haasum et al. 2012).

Table 8 presents the prevalence of psychotropic drug use in institutional settings. The prevalence of users of psychotropic drugs has varied between 36% and 80% in institutional settings, being fairly consistently >50% in prevalence studies published after the year 2000. In Norway, the prevalence of psychotropic drugs increased from 52% to 71% between the years 1985 and 2009 (Nygaard et al. 2004, Ruths et al. 2013). In other European countries, the prevalence of psychotropic drugs has varied between 52% and 85% (Olsson et al. 2010, Richter et al. 2012, Rolland et al. 2012). In Finland, the prevalence of any psychotropic drug has ranged from 71% to 80% (Hosia-Randell and Pitkälä 2005, Alanen et al. 2006, Nurminen et al. 2009). The use of psychotropic drugs in Finland has shown a trend for a decrease in nursing homes, while remaining at the same level in assisted living facilities (Pitkälä et al. 2015).

The use of antipsychotics is common, varying from 15% to up to 54% in nursing homes and other long-term care facilities in Europe and being highest in Spain (de Mauleon et al. 2014). In Norway, the use of antipsychotics remained at the same level in 1997-2009, but conventional neuroleptics use decreased and atypical use increased (Ruths et al. 2013). In Finland, the use of antipsychotics in nursing homes and other long-term care facilities has varied between 21% and 48% (Hosia-Randell and Pitkälä 2005, Alanen et al. 2006, Raivio et al. 2007, Nurminen et al. 2009, de Mauleon et al. 2014, Pitkälä et al. 2015). The prevalence of the use of antipsychotics in long-term institutional care in Finland decreased from 42% in 2001 to 39% in 2003, however, this decrease was not statistically

significant (Alanen et al. 2006). Adequate indications may not be fulfilled in all cases (Alanen et al. 2006). The use of antipsychotics is more common among patients with dementia (Raivio et al. 2007, Bell et al. 2010), and this trend is seen also in other countries (Macdonald et al. 2002, Olsson et al. 2010, Barro-Belaygues et al. 2011). Neuropsychiatric symptoms of dementia are treated with antipsychotics even though there is limited evidence of their effects (Sink et al. 2005). The use of atypical antipsychotics is nowadays more common in nursing homes than the use of conventional antipsychotics (Liperoti et al. 2003); a cross-sectional analysis of nursing homes in USA (Kamble et al. 2008), Finland (Bell et al. 2010), and Norway (Ruths et al. 2013) revealed the same trend. The use of atypical antipsychotics has also increased together with a decrease in the use of conventional antipsychotics among older patients with schizophrenia in Finland (Talaslahti et al. 2013). According to a Finnish cross-sectional study, residents with dementia used more frequently antipsychotics but less frequently antidepressants and sedative-hypnotics than residents without dementia (Bell et al. 2010). In a recent Finnish study, 36% of people in residential care were on antipsychotics and 26% on antidepressants (Kuronen 2017).

Antidepressants are also widely used among older people. Of residents in institutional settings, 12-48% are administered antidepressants (Bourgeois et al. 2012, Micca et al. 2013). In addition to treating depression, antidepressants are used for insomnia, anxiety, and neuropathic pain (Bourgeois et al. 2012). According to a randomized placebo-controlled trial, there was evidence that the antidepressants sertraline and mirtazapine might be no more effective than placebo in 13 weeks, but they may produce more adverse reactions when treating depression in Alzheimer's disease (Banerjee et al. 2013). There are also trials that show positive effects when older people with major depressive disorder (MDD) are treated with an antidepressant. According to a meta-analysis, vortioxetine treatment among people aged 55-88 years with MDD was effective and well tolerated (Nomikos et al. 2017). Major depressive symptoms may increase mortality in patients with mild dementia and depression should be treated carefully (Petersen et al. 2017). In institutional settings, the use of antidepressants has varied between 6% and 59% (Table 8). The use of antidepressants is on the rise (Nygaard et al. 2004, Hanlon et al. 2010a, Ruths et al. 2013). In Finland, the use of antidepressants in institutional settings has varied between 34% and 46% (Hosia-Randell and Pitkälä 2005, Alanen et al. 2006, Bell et al. 2010, Pitkälä et al. 2015).

The long-term use of anxiolytics, sedatives, and hypnotics is common, although it is known that they are addictive and difficult to withdraw (Ruths et al. 2013). Among community-dwelling older people, the use of benzodiazepines was associated with cognitive decline (Hanlon et al. 1998,

Puustinen et al. 2011, Puustinen et al. 2012). According to a Finnish study among home-dwelling older people, 35% with dementia and 29% without dementia used hypnotics (Hartikainen et al. 2003). The use of anxiolytics and hypnotics decreased in nursing homes in Helsinki, Finland from 41% and 11% in 2003 to 17% and 6% in 2011, respectively (Pitkälä et al. 2015). The use of anxiolytics in assisted living facilities in Helsinki has diminished from 24% in 2007 to 16% in 2011. However, the use of hypnotics remained at the same level, 10-12% (Pitkälä et al. 2015). In Norway, the use of anxiolytics and hypnotics in nursing homes increased from 1997 to 2009 (Ruths et al. 2013) (see Table 8).

The use of opioids has also been common (Berman et al. 2007, Jensen-Dahm et al. 2015, Pitkälä et al. 2015, Sandvik et al. 2016), and at least in Finland their use has been increasing, although they are used less in Finland than in other countries. Pain treatment is challenging among older people, and especially people with dementia are at very high risk for under-treatment of pain (Plooij et al. 2012). Non-steroidal anti-inflammatory drugs (NSAIDs) have adverse effects among older people (Abraham et al. 2008) and a number of drug-drug interactions (Bleumink et al. 2003, Swedish, Finnish, Interaction, X-referencing (SFINX) database). Their use has decreased (Sandvik et al. 2016), which may partly explain the increased use of opioids. In Norway, the use of opioids has increased in nursing homes from 11% to 24% between 2000 and 2011 (Sandvik et al. 2016). Similar figures are seen in nursing homes in Finland (Pitkälä et al. 2015). In an American study, 66% of residents in nursing homes or palliative care with any kind of pain received opioids (Hanlon et al. 2010b).

Table 8. Prevalence of the use of psychotropic and central nervous system medications in institutional settings [ALF=assisted living facility; LTCF(W)=long-term care facility (ward); NH=nursing home; NHD=nursing home for people with dementia; RC=residential care; RH=residential home; RU=regular units; SCU=special care units; RCT=randomized controlled trial PIP=potentially inappropriate prescribing; PRN=pro re nata; A=anxiolytics; AT=atypical antipsychotics; B=benzodiazepines; ChE=cholinesterase inhibitors; CN=conventional neuroleptics H=hypnotics; S=sedatives; SSRI= selective serotonin reuptake inhibitors; OA=other antidepressants; TCA=tricyclic antidepressants].

Study, country (setting)	N/ Females %	Age, years	Any psychotropic, %	Anti-psychotics, %	Anxiolytics (A), sedatives (S), hypnotics (H), %	Antidepressants, %	Anti-epileptics, %	Opioids, %	Anti-dementia drugs, %	Comments
Nursing homes										
Garrard et al. 1995, USA	33317/ 73%	54% ≥85	36	15	A: 12	16				Use of antipsychotics use had decreased after OBRA 87, results from 1990/1991
Schmidt et al. 1998a, Sweden	1854//70%	83	76-79	38	A: 40 H: 40					Outreach programme did not decrease the use of psychotropics
Schmidt et al. 1998b, Sweden	1823/70%	83		34	A: 42; H: 38	24				Facilities with better nursing staff and drug intervention teams had fewer deviations from appropriate prescribing
Van Dijk et al. 2000, The Netherlands	2355/71%	82	74	35	A: 28 H&S: 54	17		14		Overall drug utilization was high
Sørensen et al. 2001, Denmark	288/68%	85	56	21	B: 38	24				Behavioural problems associated with use of neuroleptics and benzodiazepines irrespective of psychiatric diagnoses
Svarstad et al. 2001, USA	1181/75% 1650/74%	83		24 16	B: 18 B: 23	17 21				1986-1989 & 1993-1994 Follow-up of OBRA High nurse/resident ratio predicted less antipsychotics
Ruths et al. 2001, Norway	1552/75%	84	59	23	B: 22	31				Marked variations in psychotropic drug use between institutions
Draper et al. 2001, Australia	647/73%	82	52	21	A: 9 S/H: 23	20				When PRN considered, 59% received ≥1, 23% ≥2, and 5% ≥ 3 psychotropics
Macdonald et al. 2002, UK	445/78%	85		14	A: 21 H: 19	25				Significant association between low MMSE and use of AP
Schmidt and Svarstad 2002, Sweden	1645/68%	84		28	A: 43 H: 39	31				Quality of drug use was associated with regular multidisciplinary team discussions
Lindesay et al. 2003, UK (LTW)	In 1997: 4226/46%	>65		22						Urinary incontinence principal adverse effect
Holmquist et al. 2003, Sweden (NH+ALF)	175/72%	87	73	17	A: 32 H: 45	33				Documentation of indications is inadequate

Table 8. Continued…

Study, country, (setting)	N/ Females %	Age, years	Any psycho-tropic, %	Anti-psycho-tics, %	Anxiolytics (A), sedatives (S), hypnotics (H), %	Antidep-ressants, %	Anti-epilep-tics, %	Opioids, %	Anti-dementia drugs, %	Comments
Nygaard et al. 2004, Norway	1035/78%	86	57	22	A: 16 H: 14	31				From 1985 to 1997, use of antipsychotics decreased, but other psychotropics increased
Gobert et al. 2005, Canada/Switzerland	C: 8183/73% S: 7592/77%	83 85	67 78	33 36	A&H: 43 A&H: 55	18 28				Comparison of psychotropic drug use between two countries
Hosia-Randell and Pitkälä 2005, Finland	1987/81%	84	80	AT: 27 CN: 19	A: 26 H: 28	45			ChEI: 10	70% diagnosed with dementia
Snowdon et al. 2005, Australia	2302/70%	83		25						80% of residents receiving antipsychotics did not have diagnosis of schizophrenia
Alanen et al. 2006, Finland (NH, RH)	In 2003: 3867/76%	83	71	39	A: 33 H: 33	42				Antipsychotic use decreased from 42% in 2001 to 39% in 2003, indication for use often unclear
Rochon et al. 2007, Canada	47322/74%	84		32						Antipsychotic prescribing varied greatly between facilities
Bergman et al. 2007, Sweden	7904/70%	85			A: 46 H-S: 55	51		32		Register analysis. Concomitantly >2 psychotropics 39%
Raivio et al. 2007, Finland (NH& LTCW)	No dementia 170/76% Dementia 254/85%	86		AT: 9 CN: 29					ChEI: 3	Sample from years 1999-2000. Users of AT had lower mortality than non-users. People with dementia had more AT and CN than those without dementia
Selbaek et al. 2008a, Norway	933 dementia /74%	85	75	26	A: 24 S: 26	39			14	Behavioural symptoms are chronically present. Long-term use of psychotropics is extensive
Selbaek et al. 2008b, Norwegian	1075/73%	SCU: 83/ RU: 85	SCU: 82 RU: 68	SCU: AT: 18 CN: 32 RU: AT: 11 CN:21	SCU: A:22 S:24 RU: A:29 S:30	SCU: 36 RU: 42				Special care unit (SCU) had patients with dementia (85%), whereas only 29% had dementia diagnosis in regular unit (RU)
Kamble et al. 2008, USA	11939/74%	>85 51%		25 AT: 23 CN: 2						Female gender and higher age negatively associated, history of falls positively associated with use of antipsychotics
Westbury et al. 2010, Australia	1591		62	21	B: 31	38				Controlled trial, aimed to reduce psychotropic use
Olsson et al. 2010, Sweden (NH&NHD)	3705/72%	85	81	26	A: 36 H/S: 51	44		32		Cross-sectional. Negative association between quality of prescribing and number of prescribers per resident

Table 8. Continued…

Study, country, (setting)	N/ Females %	Age, years	Any psycho-tropic, %	Anti-psycho-tics, %	Anxiolytics (A), sedatives (S), hypnotics (H), %	Antidep-ressants, %	Anti-epilep-tics, %	Opioids, %	Anti-dementia drugs, %	Comments
Hanlon et al. 2010a, USA	In 1996 In 2006			16 26	A: 16; S/H: 5 A: 19; S/H: 7	22 48				Use of antidepressants increased in NHs. Noteworthy is nurses' important role in influencing decisions about psychotropic medication
Patterson et al. 2010, Northern Ireland	334/73%	83	66	29	A or H 58					RCT, reduction in inappropriate psychotropic medication, no effect on falls.
Petek et al. 2011, Slovenia	2040/79%	83	73	28	A: 21 H and S: 47	23				Female gender, lower age, dementia, and depression predicted use of psychotropics.
Lustenberger et al. 2011, Switzerland	Dementia 7580/68% No dementia 11273/68%	84 83	71 55	45 17		30 27				Resident Assesment Instrument Minimum Data Set (RAI-MDS) data. Use of antipsychotics should be carefully considered
Onder et al. 2012b, eight countries	4023/73%	84		26	B: 36	36			11	SHELTER study, Czech Republic, England, Finland, France, Germany, Italy, Netherlands, and Israel. Antiparkinson drugs 8%
Rolland et al. 2012, France	2231/70%	86	70	19	A: 35 H: 30	39			24	Psychotropics, especially antipsychotics, were prescribed to patients with dementia
Richter et al. 2012, Austria and Germany	A: 1844/73% G: 1125/85% G: 2367/81%	81 87 86	75 52 52	46 28 28	A: 22; H: 13 A: 11; H: 10 A: 13; H: 11	37 20 20				3 cross-sectional samples 2004-2007 in Austria (A) and Germany (G). CN more commonly used than AT in all settings
Bourgeois et al. 2012, Belgium	1730, 78%	85	78	33	B: 53	40			8	Cross-sectional study. Use of antiparkinson drugs 11%. Depression treatment was proper.
Galik and Resnick 2013, USA	419/80%	84	69	19	A: 12 S-H: 9	59				Psychotropic medication associated with decrease in quality of life
Ruths et al. 2013, Norway	7661/73%	85	Any PT: 58→71 >2 PT: 5→ 11	23 CN: 23→8 AT: 1→12	A: 15→22 H: 15→23	32→51				6 cross-sectional samples in 1997-2009. Prescribing of psychotropics, especially antidepressants, increased. Conventional antipsychotics use decreased, atypical antipsychotics use increased
Mann et al. 2013, Austria	1844/73%	81	74	46 any AT 19 CN 38	A: 22 H: 13	36 any SSRI 30 TCA 8				55% of residents received at least one psychotropic considered PIP
Laffon de Mazières et al. 2015, France	6275, 74%			24						33.5% of patients having a neuroleptic was considered appropriate prescribing
Jensen-Dahm et al. 2015, Denmark	NH Dementia 16,048/71%	>65						38	40	Home-dwellingpatients with dementia 28% received opioids, those without dementia 17%

Table 8. Continued…

Study, country, (setting)	N/ Females %	Age, years	Any psycho-tropic, %	Anti-psycho-tics, %	Anxiolytics (A), sedatives (S), hypnotics (H), %	Antidep-ressants, %	Anti-epilep-tics, %	Opioids, %	Anti-dementia drugs, %	Comments
Pitkälä et al. 2015, Finland	NH 2003 1987/81% NH 2011 1576/77%	84 85	Mean 1.9 Mean 1.0	43 28	A: 41 H: 11 A: 17 H: 6	45 42		12 23	7 28	All nursing homes in Helsinki in 2003 and 2011. Cross-sectional. Prevalence of use of opioids had doubled
Sandvik et al. 2016, Norway	1858, 71%	86						24		Cross-sectional 2011 sample, use of opioids more than doubled from 2000, 11%
Assisted living / residential care										
Crotty et al. 2004, Australia (RC)	715/84%	84	67	24	B: 44					Baseline data from a controlled trial
Gruber-Baldini et al. 2004, USA (RC/AL)	2078/76%	52% 85+	53	21	A or H: 24	33				Of participants, 48% had dementia, 14% depression, and 13% psychotic symptoms
Stafford et al. 2011, Australia (RC)	2345/76%	87	68			36				Females were on psychotropics more often than males
Barro-Belaygues et al. 2011, France (AL)	4730/73% Dementia No dementia	 86 85		 34 23					 51	2082 residents had dementia. Of them, 51% received dementia treatment. Non-users of dementia treatment received more often antipsychotics
Pitkälä et al. 2015, Finland (AL)	AL 2007 1377/78% AL 2011 1586/78%	83 84	Mean 1.1 Mean 1.2	27 32	A: 24 H: 10 A: 16 H: 12	40 46		9 17	32 39	All assisted living facilities in Helsinki in 2007 and 2011. Residents in AL more disabled and suffered more often from dementia in 2011 than in 2007
Tan et al. 2015, Ausralia (RC)	383, 78%	88						29		Sleepiness was not associated with use of opioids
Other/multiple facilities										
Niwata et al. 2006, Japan, LTCF	1669/75%	85	19							Cross-sectional study on Beers' 2003 inappropriate medication (21%)
Lövheim et al. 2008, Sweden (geriatric care: RC, NH, LTCW, psychogeriatric etc.)	1. 3195/63% 2. 3669/68%	82 83	38 65	25, AT: 0 21, AT: 10	A: 5 S: 9 A: 14 S: 31	6 40			0 4	Cross-sectional study in 1982 and in 2000. Use of antipsychotics decreased, use of antidepressants and anxiolytics and sedatives increased
Nurminen et al. 2009, Finland (LTCW)	154/73%	84	79	48 any AT: 38 CN: 14	B: 65	26		19		33% received >2 psychotropics. Conclusion: psychotropics were used as chemical restraints

Table 8. Continued…

Study, country, (setting)	N/ Females %	Age, years	Any psycho-tropic, %	Anti-psycho-tics, %	Anxiolytics (A), sedatives (S), hypnotics (H), %	Antidep-ressants, %	Anti-epilep-tics, %	Opioids, %	Anti-dementia drugs, %	Comments
Bell et al. 2010, Finland (LTCF)	Dementia 781, 77% No dementia 271, 68%	82 78		43 any AT: 32 CN: 14 33 any AT: 21, CN: 15	A: 32 S/H: 23 A: 22 S/H: 28	36 any SSRI: 26, TCA: 2 OA: 7 46 any SSRI: 31, TCA: 5, OA: 13				Cross-sectional study. Residents with dementia received more frequently antipsychotics, but less frequently antidepressants and sedative-hypnotics
Johnell and Fastbom 2012, Sweden (Institutionalized)	86 721, 70%	86			H/S 34	44		18		Register study. Compared with the home-dwelling elderly, institutionalized older people received more psychotropics and less cardiovascular therapy
De Mauleon et al. 2014, Sweden (Sw), Finland (Fi), Netherlands (N), Germany (G), Estonia (Es), France (Fr), Spain (Sp), England (E) (LTCF)	791, 74%	84		All 37 Sw: 12 Fi: 30 N: 35 G: 47 Es: 48 Fr: 27 Sp: 54 E: 33						Inter-European study, participants were people with dementia recently admitted to LTCF. Atypical antipsychotic use was more common than conventional use in other countries, except in Netherlands and France, where conventional use was more common
Stock et al. 2017, Canada (ALF, LTCF)	AL1089/77% LTCF 1000/66%	85 85		26 32						Cross-sectional analyses. Among antipsychotic users, the proportion of potentially inappropriate use was 81% in ALFs and 70% in LTCFs
Kuronen 2017, Finland (residential care)	1439/69%	82		36 any AT: 33 CN: 7	B: 27	26 any SSRI 15 TCA 2			36	Academic dissertation. Dementia diagnosis in 56% of residents and neuropsychiatric symptoms were common

2.2.4.3 Factors associated with use of psychotropic drugs

Factors associated with the use of psychotropic drugs seem to be younger age (Draper et al. 2001, Ruths et al. 2001, Bergman et al. 2007, Kamble et al. 2008, Olsson et al. 2010, Petek et al. 2011, Ruths et al. 2013) and female gender (Draper et al. 2001, Petek et al. 2011, Ruths et al. 2013), whereas some studies suggest younger age and male gender to be associated with antipsychotic medication (Alanen et al. 2006). Potentially inappropriate antipsychotic use is more common in older age (Laffon de Mazières et al. 2015). One study found that in up to two-thirds of cases neuroleptic drug prescriptions were potentially inappropriate and one reason for this was the large number of physicians involved in patient care in nursing homes (Laffon de Mazières et al. 2015). Patients having inappropriate prescribing of neuroleptic drugs were more often ≥85 years old and suffering from dementia (Laffon de Mazières et al. 2015). Female gender seemed to be a predictor also of hypnotic or sedative drug use (Johnell and Fastbom 2011, Ruths et al. 2013) as well as use of antidepressants and SSRIs (Hosia-Randell and Pitkälä 2005, Ruths et al. 2013). However, men used more antipsychotics (Hosia-Randell and Pitkälä 2005, Ruths et al. 2013) and anxiolytics other than benzodiazepines (buspirone, clomethiazole) than women (Hosia-Randell and Pitkälä 2005). Higher number of regularly used drugs, dementia, depression, living in bigger nursing homes, and male physicians were associated with use of psychotropics (Petek et al. 2011). According to a Canadian cross-sectional study, the use of antipsychotics in both ALFs and LTCFs was associated with lower mean age, dementia, psychiatric disorders and behavioural symptoms, frailty, and use of antidepressants, and in LTCF also with hypnotic and/or sedative use, physical restraints, and history of falls (Stock et al. 2017).

When comparing residents in nursing homes with or without dementia, those with dementia received any psychotropic, any antipsychotic, and any antidepressant more often than those without dementia (Lustenberger et al. 2011). Psychotropic drug use was often associated with behavioural symptoms (Sørensen et al. 2001, Nygaard et al. 2004, Kamble et al. 2008, Petek et al. 2011, Stock et al. 2017), but not with cognitive impairment (Nygaard et al. 2004). According to the SHELTER study, overall prevalence of psychotropic use in European long-term facilities was 33%, and the strongest association with use was found with severe behavioural symptoms (Foebel et al. 2014). Hyperactive behaviour seemed to be one predictor for the use of antipsychotic medication (de Mauleon et al. 2014).

Lower MMSE was associated with the use of antipsychotics (Macdonald et al. 2002). Dementia and behavioural symptoms are predictors of nursing home placement (Phillips and Diwan 2003), and

residents having dementia with behavioural symptoms are at high risk of receiving antipsychotics (Alanen et al. 2006, Rolland et al. 2012). Nevertheless, in dementia-specific units the use of antipsychotics was more appropriate (de Mauleon et al. 2014). In Finland, one reason for high psychotropic use in institutional settings may also be the low staffing level, which in the five years preceding the study had been criticized in Finnish nursing homes (Hosia-Randell and Pitkälä 2005). Psychotropic drugs were widely used among nursing home residents despite the higher risk for adverse reactions in this population (Hosia-Randell et al. 2008).

Practitioners must also be careful when prescribing antidepressants for depression in dementia because they might not be more effective than placebo, but will have more adverse effects (Banerjee et al. 2013). However, in one review antidepressants did improve depression among people with dementia (Franco and Messinger-Rapport 2006). Antidepressants are also used to treat pain (Bourgeois et al. 2012, Micca et al. 2013) and insomnia and anxiety (Bourgeois et al. 2012). Factors associated with antidepressant use were polypharmacy, peptic ulcer, insomnia, pain, and constipation (Bourgeois et al. 2012).

2.2.4.4 Adverse events related to psychotropic drugs

Psychotropic drug groups have typical adverse effects (Rang et al. 2016). Antipsychotic drugs, especially conventional antipsychotics but also atypical antipsychotics, may cause extrapyramidal symptoms. Tardive dyskinesia is a serious and often irreversible unwanted adverse event caused by conventional antipsychotics (Rang et al. 2016) as well as atypical antipsychotics (Woods et al. 2010). Dry mouth, blurred vision, constipation, urinary retention, and sedation may occur as anticholinergic side effects. Antipsychotic drugs may also cause orthostatic hypotension and weight gain. Phenothiazines may cause jaundice. Typical antipsychotics may also cause QT-time prolongation (Aparasu et al. 2012). Clozapine use requires blood count monitoring to identify potential leucopenia and agranulocytosis, which may be fatal. Also endocrine effects may appear, such as increased plasma prolactin concentration, leading to lactation. Drowsiness and sedation are other common side effects of antipsychotics (Rang et al. 2016). Tricyclic antidepressants are chemically related to phenotiazines. Postural hypotension, dry mouth, blurred vision, and constipation may appear as side effects. There is also a risk of ventricular arrhythmias. Side effects of SSRIs include nausea, diarrhoea, agitation, insomnia, and sexual dysfunction. Mirtazapine may cause dry mouth and weight gain, mianserin agranulocytosis and aplastic anaemia. Many antidepressants also have drug-drug interactions (Rang et al. 2016). Anxiolytics and hypnotics may

cause drowsiness, sedation, confusion, impaired coordination, tolerance, and dependence (Rang et al. 2016).

According to a case-control study, the use of both conventional and atypical antipsychotic drugs among nursing home residents with dementia may increase the risk for hip fractures. Sustaining a hip fracture increases mortality among older people with dementia, and antipsychotic use-related hip fractures might be a significant contributor to this (Jalbert et al. 2010). According to a longitudinal, prospective study, concomitant use of drugs acting on the central nervous system is associated with fractures among people aged ≥65 years (Nurminen et al. 2010, Nurminen et al. 2013). Many second-generation antipsychotics are known to increase the risk of metabolic syndrome. There are only a few studies focusing on older adults, but likely the findings from younger adults apply to older people as well (Brooks et al. 2009).

According to a meta-analysis of randomized, placebo-controlled trials, atypical antipsychotics may cause such adverse effects as somnolence, urinary tract infections, incontinence, extrapyramidal symptoms and abnormal gait, increased risk for cerebrovascular events, and even increased risk for deaths when treating people with dementia (Schneider et al. 2006).

Table 9 presents the adverse outcomes of psychotropics and central nervous system drugs among residents in institutional care.

Psychotropic drugs and falls

An association exists between the use of psychotropic drugs and falls among older people. A systematic review and meta-analysis consisting of both home-dwelling and institutionalized people aged over 60 years showed that use of psychotropic drugs in combination or at higher doses increased the incidence of falls (Leipzig et al. 1999). In an Australian cohort study, olanzapine and antidepressants were significantly associated with falls, and atypical antipsychotics were not associated with fewer falls than conventional antipsychotics among nursing home and hostel residents (Hien et al. 2005). The association between falls and use of central nervous system drugs, especially psychotropic drugs, was also shown in a systematic review containing both home-dwelling and institutionalized people ≥60 years (Hartikainen et al. 2007). According to this review, especially benzodiazepines seemed to be one of the main risks for falls and fractures among older people. Also antidepressants, especially tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), may have even higher risk for falls. This review article shows also that antipsychotic drugs seem to increase risk for falls. One explanation is their extrapyramidal adverse

effects and anticholinergic properties (Hartikainen et al. 2007). In a meta-analysis, the risk for falls among institutionalized older people was increased with psychotropic drug use (Bloch et al. 2011) A cross-sectional study showed that the use of psychotropic medication in nursing homes was associated with falls (Olazarán et al. 2013). According to an observational study among 2854 home care people, use of any psychotropic drug, atypical antipsychotic drug, or benzodiazepine with a long or short elimination time increased risk for falls (Landi et al. 2005). A study among Australian community-dwelling veterans aged ≥65 years showed that use of three or four psychoactive medicines doubled the risk for falls resulting in hospitalization and use of five or more tripled the risk (Pratt et al. 2014). According to a systematic review and meta-analysis, the use of olanzapine, imipramine, mirtazapine, nortriptyline, amitriptyline, paroxetine, or trazodone was associated with increased risk of falling (Ruxton et al. 2015). The study included older people (≥65 years), both community-dwelling and institutionalized. A retrospective, longitudinal cohort study among nursing home residents with dementia suggested that the use of an antidepressant as a monotherapy was associated with higher risk of fractures and falls than the use of an antipsychotic as a monotherapy (Wei et al. 2017). The reason for this remained unclear.

Psychotropic drugs and cognition

A meta-analysis containing 15 RCTs, including 3353 patients with dementia using atypical antipsychotics and 1757 patients randomized to placebo, showed worsening in cognitive tests among drug users (Schneider et al. 2006). According to a longitudinal study, psychotropic medication (groups were all antidepressants, SSRIs, antipsychotics, and benzodiazepines) might be associated with more rapid cognitive decline in Alzheimer's disease (Rosenberg et al. 2012). There was also evidence of opioid use and cognitive decline in subjects aged 65 years or over (Dublin et al. 2015). A prospective cohort study with a 3-year follow-up found that use of benzodiazepine was associated with cognitive decline among community-dwelling older people (Hanlon et al. 1998). According to a Finnish longitudinal study, the use of opioids with benzodiazepines or any psychotropic medication or any CNS medication was associated with cognitive decline among cognitively intact older people (Puustinen et al. 2011). Another Finnish longitudinal study shows that benzodiazepines or any psychotropic drug use may be an independent risk factor for cognitive decline in cognitively disabled subjects ≥75 years (Puustinen et al. 2012). The effect of bentzodiazepines on cognition may be long-lasting or even permanent; withdrawal of benzodiazepines as a hypnotic did not improve cognitive performance among older people even after a 6-month follow-up (Puustinen et al. 2014).

Association of psychotropic drugs with use of health services and mortality

The efficacy of atypical antipsychotics for neuropsychiatric symptoms among people with dementia is limited (Schneider et al. 2006), risperidone and olanzapine having some evidence of efficacy (Sink et al. 2005, Seitz et al. 2013). It was shown in a meta-analysis that use of atypical antipsychotics compared with placebo might lead to increased mortality in patients with dementia. Most patients lived in nursing homes (Schneider et al. 2005). There have also been contrary findings. In a Finnish study, the use of conventional or atypical antipsychotic medication among older patients with dementia did not increase mortality or hospital admissions (Raivio et al. 2007). In any case, the Food and Drugs Administration (FDA) Public Health Advisory has highlighted the risk of deaths with both atypical (FDA 2013) and conventional antipsychotics among people with dementia (FDA 2010).

Conventional antipsychotics may have an even higher risk of deaths than atypical antipsychotics (Wang et al. 2005, Aparasu et al. 2012, Sikirica et al. 2013). It has been suggested that especially conventional but also atypical antipsychotics are associated with higher mortality when used to treat neuropsychiatric symptoms among outpatients with dementia (Kales et al. 2007). These patients were compared with patients using other psychiatric medication (SSRIs, other newer antidepressants, TCAs, anticonvulsants, anxiolytics/hypnotics, combinations, or no psychiatric medication) (Kales et al. 2007). Furthermore, the combination of conventional and atypical antipsychotics leads to the poorest survival (Kales et al. 2007). A retrospective cohort study among nursing home residents also found that use of conventional antipsychotics was associated with a higher risk of mortality than use of atypical antipsychotics (Liperoti et al. 2009).

Cardiovascular adverse effects like QT-time prolongation, anticholinergic effects, extrapyramidal symptoms, and infections might be explanations for increased mortality risk in the use of typical antipsychotics (Aparasu et al. 2012). Due to the risk of sudden cardiac death, cardiovascular status and electrocardiography (ECG) monitoring are needed when treating older people with antipsychotic drugs (Narang et al. 2010). The risk of sudden cardiac death was increased even in a younger population using antipsychotics (Ray et al. 2001). Cardiovascular and cerebrovascular risk factors may be the link to the increased risk of death with conventional antipsychotics (Liperoti et al. 2009). A retrospective case-control study suggests that the effect of antipsychotics on mortality in elderly patients with dementia may be even higher than previous studies indicate, and it appears to be dose dependent (Maust et al. 2015).

Older people with schizophrenia have a higher mortality than the general age- and gender-matched population (Talaslahti 2015). The most common causes of death (e.g. cardiovascular, neoplasms) were the same, but unnatural causes (e.g. suicides, accidents) were 11-fold. The risk of psychiatric hospitalization was associated with antipsychotic polypharmacy and the use of antidepressants (Talaslahti 2015).

A cohort (SHELTER) study investigated antipsychotic drug interactions and mortality among older nursing home residents with cognitive impairment in seven European Union countries and Israel (Liperoti et al. 2017). Antipsychotic drug interactions were observed in 46% of participants receiving antipsychotics, 11% of whom were exposed to two or more interactions (Liperoti et al. 2017). Antipsychotic drugs interactions were associated with higher mortality also after adjusting for potential confounders (Liperoti et al. 2017).

A random sample of demented older people, 44% of them institutionalized, showed that especially use of antipsychotics and also concomitant use of any kind of psychotropic drugs was a risk factor for death compared with non-use of psychotropic drugs (Hartikainen et al. 2005).

On the other hand, intensive care of depression in older adults, including both optimal antidepressant use and psychotherapy, decreased mortality relative to usual care (Gallo et al. 2013). In one analysis of residents of long-term care facilities, the concurrent use of three or more psychotropic drugs was not associated with an increased risk of mortality (Bell et al. 2009). Sedative load was not a significant risk for deaths among residents in long-term care facilities (Taipale et al. 2009).

According to a recent Norwegian longitudinal (75-month follow-up) study among nursing home residents, neither use of antipsychotics nor other psychotropics was associated with increased risk of mortality (Selbaek et al. 2016).

Psychotropic drugs and quality of life

A secondary data analysis of an RCT in nursing home residents explored the use of psychotropics and its association with physical and psychosocial outcomes (Galik and Resnick 2013). Those residents not on psychotropics (all psychotropics) had significantly better functional outcomes ($p=0.01$), and a trend ($p=0.05$) was observed of a better overall quality of life compared with psychotropic users (Galik and Resnick 2013). According to a longitudinal study, the use of

antipsychotic medication might not decrease the quality of life among nursing home residents, however, neuropsychiatric symptoms do negatively affect the quality of life (van de Ven-Vakhteeva et al. 2013). Antidepressant use had a positive impact on quality of life like positive self-image and negative affect (van de Ven-Vakhteeva et al. 2013). The use of antipsychotics among residents with schizophrenia in long-term institutional care was associated with a severe degree of functional impairment (Alanen 2007).

Table 9. Outcomes of the use of antipsychotics and multiple use of sedative drugs among residents in institutional care.

Study, country	N, characteristics of sample	Study design	Studied medications	Findings	Comments
Hospitalizations					
Raivio et al. 2007, Finland	254 patients with dementia in NH and GW. 41% 85+ years, 81% females	Cross-sectional drug use at baseline, 2-year follow-up	Antipsychotics in regular use (37% were on conventional neuroleptics, 11% on atypical antipsychotics)	Non-users had more hospital admissions than antipsychotic users	Conventional neuroleptics did not increase hospital admissions, whereas atypical antipsychotics decreased hospital admissions
Mortality					
Hartikainen et al. 2005, Finland	137 people with dementia, Of them, 44% institutionalized. Mean age 85 years, 79% females	137 patients with dementia assessed thoroughly. 5-year follow-up for mortality.	All psychotropic drugs (71% on any psychotropic drug, 48% on antipsychotics)	Antipsychotic users (HR 2.75) and users of several psychotropic drugs (HR 1.76) had increased mortality compared with non-users.	Although small sample size, study shows high risk of death among both antipsychotic users and multiple psychotropic users
Schneider et al. 2005, USA	3353 patients on atypicals, 1757 patients on placebo. Both NH and outpatients. Mean age range 77-84 years, female range 56-80%	Meta-analysis of 15 randomized placebo-controlled trials on atypicals vs. placebo among patients with dementia	Atypical antipsychotics (aripirazole, olanzapine, quetiapine, risperidone) vs placebo. Trial duration 10-16wks.	Atypical antipsychotics may be associated with an increased risk for deaths (OR 1.54).	Death rate 3.5% among atypical users vs. 2.3% among placebo users. NNH 100. Atypical antipsychotic use increased the risk for cerebrovascular adverse events
Wang et al. 2005, USA	22 890 antipsychotic users aged ≥ 65 years in Pennsylvania drug register (hospital patients, NH, outpatients). Mean age 83 years, 81% females.	Retrospective register study, 180-day follow-up	Atypical and conventional antipsychotics	Conventional antipsychotics had an even higher risk of deaths than atypicals (RR 1.37)	The first study to show that conventional antipsychotics are not safer than atypical antipsychotics
Raivio et al. 2007, Finland	254 patients with dementia in NH and GW. 41% 85+ y, 81% females	Cross-sectional drug use at baseline, follow-up for 2 years	Antipsychotics in regular use (37% on conventional neuroleptics, 11% on atypical antipsychotics)	Atypical antipsychotic users had lower risk of mortality than non-users, among conventional users no difference from non-users	Small sample size, protective effect of atypicals was seen only in multivariate analysis
Gill et al. 2007, Canada	Total of 8079 matched pairs in long-term care. Mean age 85, 72% females. All suffered from dementia.	Retrospective case-control study, follow-up 180 days	Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use	New use of atypicals was associated with risk of death at 30 days compared with non-users (HR 1.55).	Relative to atypicals conventional use was associated with higher risk of death

Table 9. Continued…

Study, country	N, characteristics of sample	Study design	Studied medications	Findings	Comments
Liperoti et al. 2009, USA	9729 NH-patients with dementia. Mean age 84, 72% females	Retrospective cohort study, follow-up 6 months	New users of atypical (n=6524) and conventional antipsychotics (n=3205)	Rate of deaths was increased for users of conventional antipsychotics (HR 1.26; 95% CI 1.13 to 1.42) compared with atypical antipsychotics	Study uses MDS database
Bell et al. 2009, Finland	1087 long-term care hospital patients. Mean age 81, 75% females	Cross-sectional drug use and diagnostic data at baseline, 5 y mortality	Concurrent use of three or more psychotropic drugs	Concurrent use of >2 psychotropic drugs was not associated with increased mortality (HR 1.16, 95% CI 0.97 to 1.38)	Analyses adjusted for age, gender, comorbidities, nutritional status, mobility
Taipale et al. 2009, Finland	1004, long-term care hospital patients. Mean age 81, 75% females	Cross-sectional drug use and diagnostic data at baseline, 5 y mortality	Sedatives and drugs with sedation as a side effect or preparations with a sedating component	Sedative load was not a predictor for risk of death in multivariate adjusted analyses	Higher sedative load was associated with increased survival in univariate analysis
Aparasu et al. 2012, USA	7218, NH Mean age 83, 65% females	Retrospective register study, follow-up 6 months	Conventional antipsychotic users (n=3609) were compared with atypical antipsychotic users (n=3609)	Conventional antipsychotic users had higher risk of death than users of atypicals (HR 1.41, 95% CI 1.27 to 1.57)	Risk was higher during the first 40 days of treatment than during 40-180 days of treatment
Liperoti et al. 2017, 7 European countries and Israel	604, 59 NHs. Mean age 83, 72% females	Retrospective longitudinal cohort study, 2009 to 2011	Antipsychotic users. Antipsychotic DDIs and their association with mortality were studied	Antipsychotic DDIs associated with higher mortality than antipsychotics without antipsychotic drug interactions	Caution in antipsychotic use, especially among older people concomitantly receiving cardiovascular or psychotropic medication
Falls					
Leipzig et al. 1999	People aged 60 and over	Systematic review and meta-analysis of 40 studies	Sedative/hypnotic, antidepressant, or neuroleptic use	Small, consistent association between use of psychotropic drugs and falls	Only part of the population was in long-term care
Hien et al. 2005, Australia	2005: 898 NH residents (high-level care facilities), 1107 from hostels (intermediate-level care facilities)	Prospective cohort study, 1-month follow-up	All psychotropic drugs	After adjusting for other psychotropics and other risk factors for falls, olanzapine and antidepressants (50% of antidepressants SSRIs) were significantly associated with falls	Atypical antipsychotics were not associated with fewer falls than older antipsychotics

Table 9. Continued…

Study, country	N, characteristics of sample	Study design	Studied medications	Findings	Comments
Hartikainen et al. 2007	MEDLINE, original English articles 1/1996-12/2004 and Cochrane library, 29 studies remained	Systematic review	Medication associated with falls	Central nervous system drugs, especially psychotropic drugs, were associated with an increased risk for falls	NH, LTCW, hospital patients, rehabilitation, residential care, community dwelling
Bloch et al. 2011	177 studies included	Review and meta-analysis	Antidepressants, benzodiazepines, hypnotics, neuroleptics, tranquillizers	Association exists between falls in the elderly and psychotropic drug use	Age over 60 years, both institutionalized and ambulatory patients
Olazarán et al. 2013, Spain	4502, private Spanish nursing homes	Cross-sectional study	Psychotropic drugs	Psychotropic drugs were highly prescribed and were associated with falls	Most unsafe were long half-life BZDs, neuroleptics, and psychotropics in combination
Quality of life, other adverse events					
Schneider et al. 2006, USA	3353 AT, 1757 placebo. Trials (15) were selected by consensus of the authors. Most nursing homes, also outpatients. Patients with dementia.	Meta-analysis of randomized placebo-controlled trials	Atypical antipsychotics versus placebo	Adverse events somnolence, urinary tract infections or incontinence, extrapyramidal symptoms, abnormal gait. Cognitive tests declined	Atypical antipsychotics were associated with many harmful effects. Medication should be carefully calibrated, maximazing efficacy and minimizing adverse events.
van de Ven-Vakhteeva et al. 2013, Netherlands	290, NH	Longitudinal study in dementia special care units	Antipsychotics, anxiolytics, hypnotics, antidepressants	Antipsychotic prescriptions did not significantly change participants' QoL, antidepressant use positively affected some aspect of QoL, positive self-image and negative affect	

AT=atypical; BZD=benzodiazepines; CI=confidence interval; DDI=drug-drug interaction: pharmacodynamics e.g. QT-prolongation, neutropenia and agranulocytosis, sedation, anticholinergic side effects and pharmacokinetic interactions: induction or inhibition of cytochrome 450; HR= hazard ratio; GW=geriatric ward; LTCW=long-term care wards; MDS=Minimum Data Set; NH=Nursing home; NNH=number needed to harm; OR=Odds ratio; QoL=Quality of Life; RR=relative risk; SSRI=selective serotonin reuptake inhibitor

2.2.5 Proton pump inhibitors (PPIs)

Proton Pump Inhibitors (PPIs) are one of the most frequently prescribed drug classes in the world (Forgacs and Loganayagam 2008). PPIs have proven to be very effective drugs in the treatment of gastro-oesophageal reflux with associated complications and dyspeptic conditions (Forgacs and Loganayagam 2008). Furthermore, PPIs are commonly used to protect against gastrointestinal bleedings among users of NSAIDs, low-dose aspirin, anticoagulants, corticosteroids, or serotonin reuptake inhibitors (Lanza et al. 2009, AGS 2015, Niu et al. 2016). However, they are widely overused, especially in nursing homes. Of patients taking these drugs, 25-70% do not have an appropriate indication for use, and many drug-related problems are associated with the use of PPIs (Forgacs and Loganayagam 2008).

Several criteria for potentially inappropriate medications (PIMs) have included PPIs in their lists. PPIs are mentioned in Swedish recommendations for older people's medication (Socialstyrelsen 2010). The use of PPIs should be reviewed periodically and they should not be used without an appropriate indication. The STOPP and START criteria limited full dosage of PPI use to 8 weeks (Gallagher et al. 2008), and Beers' list 2015 does not recommend PPI use >8 weeks in high-risk patients (AGS 2015).

Long-term use of PPIs may lead to decreased absorption of vitamin B12, vitamin C, iron, calcium, and magnesium (Arkkila 2015, Teramura-Grönblad 2017). There is evidence that use of acid-suppressive drugs, such as H2 receptor antagonists (H2RAs) and PPIs, is associated with increased risk of pneumonia, probably by reduction of gastric acid secretion, allowing spread of oral infections (Laheij et al. 2004). There is also an association between the use of PPIs and enteric infections, including *Clostridium difficile* infections (Leonard et al. 2007). The FDA has made a safety announcement about this risk (FDA 2012). According to a meta-analysis containing 17 RCTs, the use of PPIs was associated with an elevated risk of cardiovascular events in patients with gastro-oesophageal reflux disease (GERD). High risk occurred especially in the omeprazole subgroup and in long-term treatment (Sun et al. 2016). Another meta-analysis found that combination use of clopidogrel with PPIs might increase the risk of major adverse cardiovascular events among patients with coronary artery disease (Niu et al. 2016). This effect was seen only with patients with a certain clopidogrel metabolizing P450 enzyme allele (Niu et al. 2016).

According to a retrospective case-control study, patients with hip fractures were more likely than controls to have received PPIs or H2RAs over the 2-year period preceding the fracture, and the risk

for hip fracture decreased after discontinuation of the drug. This association was seen only among persons who had additional risk factors for hip fractures such as alcohol abuse, arthritis, diabetes, kidney disease, or glucocorticoid use (Corley et al. 2010). A meta-analysis of studies with cohort and case-control design found an association between the use of PPIs and hip fractures, spine fractures, and fractures overall (Zhou et al. 2016). The mechanism underlying the effect of PPI use on risk of fracture is unknown. One hypothesis is that PPIs decrease calcium absorption, which leads to decrease in bone mineral density. PPI use may also induce hypomagnesemia, which might increase fracture risk (Zhou et al. 2016).

A cross-sectional study (n=1987) suggested that the use of PPIs is independently associated with diarrhoea (Teramura-Grönblad et al. 2010). In a cross-sectional Finnish study consisting of 2818 residents in assisted living facilities (ALFs), long-term care hospitals (LTCHs), and acute geriatric wards (AGWs), after adjustment, the use of PPIs was associated with increased mortality in LTCHs and AGWs, but not in ALFs (Teramura-Grönblad et al. 2012).

2.2.6 Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are used for pain especially in inflammatory disorders, however, they are considered to be one of the medications most commonly causing adverse reactions among older people (Boparai and Korc-Grodzicki 2011). In Sweden, they are deemed inappropriate for older people because they may cause gastrointestinal ulcers and bleeding, fluid retention, heart failure, and renal dysfunction (Socialstyrelsen 2010). STOPP and START criteria define NSAIDs as inappropriate medication due to their unwanted effects on renal function, gastrointestinal bleeding, hypertension, and heart failure (Gallagher et al. 2008). In the last two updated Beers' criteria, they were included in the inappropriate list (AGS 2012, AGS 2015).

According to a review article, the use of NSAIDs in treatment of older adults with osteoarthritis may lead to adverse effects such as renal insufficiency and gastrointestinal toxicity (O'Neil et al. 2012). There is also some evidence of cardiovascular adverse events, thus, the use of NSAIDs should be limited to short-term use only (O'Neil et al. 2012).

NSAIDs inhibit the enzymes cyclo-oxygenase (COX) 1 and 2, leading to a decrease in prostaglandin synthesis (Bleumink et al. 2003). Under normal conditions, prostaglandins do not significantly affect renal circulation. However, when effective circulating volume is decreased, such as in heart or renal failure or dehydration, renal prostaglandins increase renal blood flow and enhance excretion of sodium and water (Bleumink et al. 2003). If prostaglandin synthesis is

inhibited with NSAIDs, another type of renal enzyme, angiotensin II, may produce excessive vasoconstriction and a decline in renal blood flow and glomerular filtration rate, potentially resulting in acute renal failure (Bleumink et al. 2003). Water and sodium retention may lead to cardiac failure. NSAIDs influence cardiovascular homeostasis with an effect on renal function, and COX-2 selective inhibitors may apparently also induce heart failure in susceptible patients (Pitkälä et al. 2002b, Bleumink et al. 2003).

The use of NSAIDs negatively influences the antihypertensive effects of thiazides, loop diuretics, α-adrenergic blockers, β-adrenergic blockers, and ACE inhibitors. If a patient is hypovolemic, NSAIDs may lower the effect of diuretics and lead to fluid retention (Bleumink et al. 2003).
In addition, there is evidence that exposure to NSAIDs with the longest half-life may be associated with an increased risk of chronic renal disease (Ingrasciotta et al. 2015). Use of NSAIDs has been found to be responsible for peptic ulcer among older people (Griffin et al. 1988). According to a study including patients aged 60+ years hospitalized for bleeding gastric or duodenal ulceration, NSAID use together with some independent risk factors, such as previous peptic ulcer, heart failure, use of oral anticoagulants or corticosteroids, diabetes, and smoking, account for 80% of the predisposing factors for ulcer bleeding (Weil et al. 2000).

There is also some evidence for increased mortality. In a retrospective cohort study among veterans aged 65+ years, an association emerged between mortality following gastrointestinal or cardiovascular events and proportion of time receiving NSAIDs or COX-2 selective NSAIDs (Abraham et al. 2008). According to a recent review and meta-analysis, the use of NSAIDs was associated with an increased risk of acute myocardial infarction (Bally et al. 2017).

2.3 Educational intervention studies to reduce harmful drug use in institutional settings

A number of randomized controlled trials, both educational interventions and medication reviews by pharmacists, have been performed to reduce the use of PIMs (Forsetlund et al. 2011). These interventions may reduce PIM use among nursing home residents. However, many of these studies have been of low quality and include a risk of bias (Forsetlund et al. 2011). Table 10 summarizes the studies aimed at reducing PIM use.

RCTs are cluster randomized, meaning that units are randomized instead of single residents.

In USA, Avorn and colleagues performed a cluster RCT, aimed at reducing psychoactive medication use in nursing homes. Physicians, nurses, and nursing assistants of intervention homes received an educational programme focused on geriatric psychopharmacology (Avorn et al. 1992). In the intervention homes, the use of psychoactive medication decreased significantly. Antipsychotic drugs and diphenhydramine had been discontinued significantly more often in intervention than control homes (Avorn et al. 1992). There was also a trend for an improvement in some cognitive tests. However, there was an increase in residents' reports of depression in the intervention homes. Despite the reduction in antipsychotic use in intervention nursing homes, there was no significant increase in behavioural disorders among residents (Avorn et al. 1992).

An educational RCT was conducted to reduce antipsychotic use and to identify factors predicting antipsychotic withdrawal or dose reduction (Meador et al. 1997). Nursing homes were the units that were randomized and analysed. Education started with a 45- to 60-minute session held by the study geropsychiatrist for physicians in which antipsychotics and other psychotropics were discussed, followed by educational activities for nursing home staff. Nursing staff received education by a trained nurse-educator and written instructions were also provided (Meador et al. 1997). This intervention resulted in a 23% reduction in days on antipsychotics in the intervention homes relative to control homes ($p=0.014$). Of patients continuing use, 25% had a dosage reduction of 50% or more. There was no increase in behavioural symptoms or use of benzodiazepines or antidepressants.

An RCT was performed in Swedish nursing homes to explore the effects on both the quantity and quality of psychotropic drug prescribing (Schmidt et al. 1998a). Nursing homes were randomized. In intervention homes, a trained pharmacist spent one day per month over a 12-month period to enhance communication in teams about drug use. The programme focused on improving teamwork of physicians, pharmacists, selected nurses, and nursing assistants. Drug use of individual residents was discussed. The intervention resulted in a significant decrease in prescribing of antipsychotics, benzodiazepine hypnotics, and TCAs, but antidepressant use increased (Schmidt et al. 1998a). Results were collected one month before the study and at the end of the 12-month intervention.

In an Australian RCT, nursing staff received problem-based education for 11 hours in each intervention NH with support of telephone calls, wall charts, bulletins, and clinical pharmacy visits, averaging 26 contact hours per intervention home. Individual medical reviews were performed and were available to the resident's physician (Roberts et al. 2001). The intervention resulted in significantly decreased use of benzodiazepines, NSAIDs, laxatives, and histamine H2-receptor antagonists. Drug use in the intervention group diminished by 15% compared with controls, thus

decreasing drug costs (Roberts et al. 2001). However, no significant changes were observed in mortality, hospitalizations, adverse events, or the disability index (Roberts et al. 2001).

Another Australian RCT aimed to improve the implementation of evidence-based clinical practice with outreach visits in order to reduce falls and prevent strokes (Crotty et al. 2004). The intervention consisted of two 30-minute visits by a pharmacist to physicians. Evidence-based guidelines on fall prevention, psychotropic drug prescribing, and stroke prevention, such as blood pressure monitoring and use of aspirin in residents with increased stroke risk and the use of warfarin in residents with atrial fibrillation, were implemented (Crotty et al. 2004). There was no difference in the use of psychotropic drugs between groups, except that the use of "as needed" antipsychotics was significantly higher in the intervention group than in the control group (relative risk (RR) 4.95; 95% CI 1.69 to 14.50) (Crotty et al. 2004). There was no difference in falls between the groups. However, number of falls increased in both groups, which may be due to their better documentation. No difference emerged between the groups in recording of high blood pressure (>140/90 mmHg) or use of aspirin or warfarin (Crotty et al. 2004).

In Great Britain, nursing home staff was trained to reduce the use of neuroleptics among residents with dementia (Fossey et al. 2006). At the beginning of the study, a consultant old age psychiatrist and a senior member of the nursing staff reviewed residents' medication in all participating nursing homes. Prescribing physicians received recommendations to stop inappropriate neuroleptics and also telephone calls if this was not implemented within two weeks. After randomization, the staff of intervention homes received training for two days a week for 10 months. Training focused on person-centred care and good treatment practices as an alternative to treating behavioural symptoms with neuroleptics (Fossey et al. 2006). At 12 months, the proportion of residents on neuroleptics was significantly lower in intervention homes than in control homes. No difference was observed between groups in the use of other psychotropics or in falls, agitation, aggression, quality of life, or well-being (Fossey et al. 2006).

In Tasmania, a controlled trial was performed with the aim to reduce the use of antipsychotics and benzodiazepines among nursing home residents (Westbury et al. 2010). Nursing home physicians received one session concerning psychotropic use, and nursing home staff received two sessions. The intervention consisted also of newsletters every other month and an educational pamphlet for relatives and residents. Two pharmacist's medication audits and feedback cycles were included. The intervention resulted in benzodiazepine use decreasing from 32% to 27% ($p<0.005$), and

antipsychotic use decreasing from 20% to 19% ($p<0.05$) in intervention homes, whereas in control homes no change in the use of these medications occurred (Westbury et al. 2010).

An RCT was performed in Spain, where nursing home physicians received education on older people's medication for 10 hours (García-Gollarte et al. 2014). The physician educational programme was followed by on-demand support (prescription advice) by phone. As a result of intervention, the mean number of inappropriate drugs according to STOPP criteria was higher in the control group than in the intervention group. In addition, the proportions of residents with polypharmacy, antipsychotics, and duplicate medication were higher in the control group than in the intervention group (García-Gollarte et al. 2014). The number of fallers increased significantly in the control group, but did not change in the intervention group. The number of residents with delirium increased in the control group and decreased in the intervention group. Use of physician and nurse visits did not change in the control group (-0.22, $p=0.3$), but decreased significantly in the intervention group (-0.76, $p=0.01$). Emergency room visits and days in hospital increased in the control group, but remained unchanged in the intervention group (García-Gollarte et al. 2014). Results are from the 3-month period after the intervention.

Summary of studies (see Table 10).

A recent RCT from Israel showed that pharmacist review followed up by recommendations may decrease the number of drugs used by frail older people (Frankenthal et al. 2014). It also suggested a decline in falls, but no change in hospitalizations, QoL, or ADL according to the Functional Independence Measure (FIM) among participants. Several other RCTs have been performed among nursing home residents in which the intervention is based on pharmacist review of residents' medication (Furniss et al. 2000, Zermansky et al. 2006, Patterson et al. 2010). They are not included in Table 10 since education is not a part of the intervention.

A recent Cochrane review on interventions to optimize prescribing in institutional care included 12 RCTs (N=10953) (Alldred et al. 2016). Besides educational interventions targeted at professionals, the interventions included organizational interventions (e.g. medication review services), case conferencing, and information and communication technology. Evidence suggested that medication appropriateness improved, but no effect was seen on adverse drug events (Alldred et al. 2016). The influence on hospitalizations, falls, QoL, and mortality was not clear (Alldred et al. 2016).

Table 10. Educational intervention studies to reduce the use of potentially inappropriate medications (PIMs) in institutional settings.

Study, country	Number (N), I, C Setting, study design	Age/ Females %	Intervention	Learning theory/ method	Results	Comments
Avorn et al. 1992, USA	I=349, C=329 NH, cluster-RCT, 5-month follow-up, aim to reduce the use of psychoactive medication	N.A.	Educational programme focused on geriatric psychopharmacology, physicians, nurses, and nursing assistants, three visits	Based on principles of "academic detailing"	Mean psychoactive drug use score was significantly reduced in intervention group compared with control group	There was trend suggesting greater improvement in some cognitive functions. Residents' depression significantly increased. No increase occurred in reports of behavioural disorders
Meador et al. 1997, USA	I=575, C=577 NH, cluster-RCT, 100-day follow-up, aim to reduce antipsychotic use and identify factors predicting withdrawal or dose reduction	I 83 years F 76% C 84 years F 79%	Physicians, nurses, nursing assistants and other direct care staff received structured guidelines for management of behavioural symptoms; 5-6 sessions	Active educational programme	Use of antipsychotics: in intervention homes, 23% reduction compared with control homes	No increase in behavioural symptoms or use of benzodiazepines or antidepressants after withdrawal
Claesson and Schmidh 1998 Schmidt et al. 1998a, Sweden	I=626, C=1228 NH cluster-RCT, 13-month follow-up, aim to affect quantity and quality of psychotropic drug prescribing	I 83 years F 70% C 84 years F 67%	Teamwork among physicians, pharmacists, staff nurses and nursing assistants. Team meetings and discussions on drug therapy for 12 months, once a month	No theory	In intervention homes, significant decrease in use of antipsychotics, benzodiazepine hypnotics, and antidepressants	Use of acceptable (SSRIs instead of TCAs) antidepressants increased in both intervention and control homes
Roberts et al. 2001, Australia	I=905, C=2325 NH, cluster-RCT, 24-month follow-up, aim to change drug use, mortality, morbidity, and costs	N.A.	Problem-based nurse education 11 hours/home, individualized medical reviews, support and visits of pharmacist	Problem-based education	Use of harmful drugs, e.g.benzodiazepines, laxatives, and NSAIDs, decreased. Costs of drugs decreased	No effect on morbidity or survival
Crotty et al. 2004, Australia	I=381, C=334 RCS (Australian hostels (low-level care) and NH (high-level care), cluster-RCT, 7-month follow-up, aim to assess the effect of outreach visits on fall reduction and stroke prevention	I 85 years F 86% C 83 years F 82%	Education, physicians received 2x30 min sessions on fall prevention, evidence-based drugs for stroke prevention and FA treatment, reduction in use of psychotropics. Other medical staff was also educated	No theory	Number of falls increased in both groups; no difference between the groups. No influence on use of drugs, with exception of "as required" antipsychotics, which increased in intervention group after the intervention	Better documentation of falls may be the reason for the increase in number of falls

Table 10. Continued…

Study, country	Number (N), I, C Setting, study design	Age/ Females %	Intervention	Learning theory	Results	Comments
Fossey et al. 2006, Great Britain	I=181, C=168 NHD, cluster-RCT, 12-month follow-up, aim to change clinical practices to reduce the use of neuroleptics	I 82 years F 35 % C 82 years F 39%	Staff received training in person-centred care and skills, supervising weekly over the study period	Individualized psychological intervention	Use of neuroleptics was significantly lower in intervention group after follow-up (19% decrease). No significant differences in levels of agitated or disruptive behaviour between I and C homes	No significant difference in use of other psychotropic drugs or in number of fallers
Westbury et al. 2010, Tasmania	I=898, C=693 controlled trial, NH, 6-month follow-up	N.A.	Pharmacist-led intervention. NH physicians received education, nursing staff received two training sessions, newsletters, interdisciplinary communication	Partly basen on academic detailing	Use of antipsychotics and benzodiazepines decreased significantly in intervention group, no chance in control group	No other outcomes were measured
Frankenthal et al. 2014 Israel	I=160, C=146; RCT, chronic care geriatric facility, 12-month follow-up	I 50% 85y+ F 71% C 44% 85y+ F 63%	Pharmacist review with STOPP/ START followed with recommendations to chief physician	No theory	Mean number of drugs decreased in intervention group and increased in control group. Mean number of falls decreased significantly in intervention group	No effects on hospitalizations, ADL, or QoL
García-Gollarte et al. 2014, Spain	I=344, C=372 NH, cluster RCT, 9.month follow-up, aim to reduce the use of inappropriate medication and improve health outcomes	I 84 years F 74 % C 84 years F 72%	Nursing homes' physicians received 10 hours of educational programme and support by phone during 6 months, medications were reviewed 3 months after the intervention	Structured education	Improvement in medication, delirium decreased significantly in the intervention group, no significant change in falls. Reduction in use of health care resources in intervention group	Number of falls and delirium increased significantly in control group

Cluster randomization=units randomized instead of individuals; FA=fibrillatio atriorum; I=intervention group; C=control group; N.A.=not applicable; NH=nursing home; NHD= nursing home for people with dementia; NSAID=non-steroidal anti-inflammatory drug; RCS=residential care setting

2.4 Summary of PHMs

There are multiple definitions for PHMs (Spinewine et al. 2007). Beers' criteria were the first explicit criteria aimed at decreasing the use of inappropriate drugs among nursing home residents (Beers et al. 1991). The criteria defined drugs as inappropriate if their adverse effects exceeded their benefits, if they lacked efficacy, or if there was a safer alternative available. These criteria and their updated versions (Beers 1997, Fick et al. 2003, AGS 2012, AGS 2015) have been criticized for being US based, and many PIM criteria have been developed in other countries. However, Beers' criteria are internationally well known. The use of PIDs according to Beers' criteria is common and has ranged from 17% to 83% in institutional settings. In a systematic review, the use of Beers' PIDs was associated with adverse drug reactions but not with quality of life (Jano and Aparasu 2007). The effect on hospitalizations and mortality is unclear (Klarin et al. 2005, Perri et al. 2005, Jano and Aparasu 2007, Price et al. 2014).

Drugs with anticholinergic properties (DAPs) block cholinergic muscarinic receptors. Permeability of the blood-brain barrier increases in old age. In addition, the ageing brain is vulnerable to toxic effects of DAPs (Ehrt et al. 2010). There are many scales to define DAPs and to measure anticholinergic burden (Han et al. 2001, Ancelin et al. 2006, Carnahan et al. 2006, Hilmer et al. 2007, Boustani et al. 2008, Chew et al. 2008, Rudolph et al. 2008, Ehrt et al. 2010, Sittironnarit et al. 2011). The prevalence of DAPs varies markedly depending on the criteria used (Salahudeen et al. 2015). Their use is associated with adverse events such as hospital admissions and fall-related hospitalizations (Salahudeen et al. 2015). Contradictory results have emerged about the relationship between DAP use and mortality (Wilson et al. 2012, Ruxton et al. 2015). Many studies have shown that DAP use is associated with cognitive decline (Rudolph et al. 2008, Campbell et al. 2009, Cancelli et al. 2009, Uusvaara et al. 2013, Gray et al. 2015, Ruxton et al. 2015).

Centrally affecting drugs, including psychotropics, are commonly used among older people (Gruber-Baldini et al. 2004, Hosia-Randell and Pitkälä 2005, Nurminen et al. 2009, Bourgeois et al. 2012, Pitkälä et al. 2015). They are used, for example, to treat neuropsychiatric symptoms in dementia, which are common in institutional settings (Sørensen et al. 2001, Foebel et al. 2014). The prevalence of psychotropics ranges from 36% to 80% in institutional settings. Antipsychotic drug use is associated with risk of fractures (Nurminen et al. 2010, Nurminen et al. 2013) and hip fracture (Jalbert et al. 2010). Use of psychotropics, including antipsychotics, antidepressants, and

benzodiazepines, may lead to falls (Hartikainen et al. 2007). Antipsychotic drug use may lead to cerebrovascular adverse events among people with dementia (Schneider et al. 2005). The use of atypical or conventional antipsychotics may also increase mortality among people with dementia (Schneider et al. 2006, Aparasu et al. 2012, Sikirica et al. 2013). Use of antipsychotics among patients with dementia may also lead to cognitive decline (Schneider et al. 2006, Puustinen et al. 2012). Attention has been paid to excessive use of psychotropics. The Omnibus Budget Reconciliation Act of 1987 in the USA (OBRA 87) improved the quality of care in US nursing homes (Omnibus Budget Reconciliation Act of 1987, Garrard et al. 1995). In addition, there are criteria in other countries regulating the use of psychotropics. For example, in Sweden the concomitant use of >2 psychotropics is considered inappropriate (Socialstyrelsen 2010).

Proton pump inhibitors (PPIs) are effective in dyspeptic conditions. However, they are overused and often lead to drug-related problems (Forgacs and Loganayagam 2008). Long-term use of PPIs may lead to malabsorption of vitamin B12 and calcium (Arkkila 2015, Teramura-Grönblad 2017). Use of PPIs is also associated with increased risk of pneumonia (Laheij et al. 2004), enteral infections such as *Clostridium difficile* (Leonard et al. 2007), and fractures (Zhou et al. 2016). Long-term use of PPIs is mentioned in several criteria of inappropriate medications for older people (Gallagher et al. 2008, Socialstyrelsen 2010, AGS 2015). Their use, both the indication and the length of use, should be reviewed periodically.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used for treatment of pain. Among older people, they are one of the medications most commonly causing unwanted effects (Boparai and Korc-Grodzicki 2011). They may cause gastrointestinal ulcers and bleeding (Griffin et al. 1988, Gallagher et al. 2008, Socialstyrelsen 2010, O'Neil et al. 2012), fluid retention and heart failure (Pitkälä et al. 2002b, Bleumink et al. 2003, Gallagher et al. 2008, Socialstyrelsen 2010), and renal failure (Pitkälä et al. 2002b, Bleumink et al. 2003, Gallagher et al. 2008, Socialstyrelsen 2010, Ingrasciotta et al. 2015). Potentially harmful medications for older people include NSAIDs according to several different criteria (Gallagher et al. 2008, Socialstyrelsen 2010, AGS 2012, AGS 2015).

In summary, there are many ways to define drugs that should not be used among older people. There is no consensus about the best criteria. The latest Beers' 2015 criteria include drugs that are also included in the criteria used here: psychotropics, DAPS, PPIs, and NSAIDs. Use of potentially inappropriate medication is associated with adverse effects as well as adverse events such as falls, fractures, infections, hospitalizations, cerebrovascular events, and even mortality.

Educational intervention studies have been performed in institutional settings to reduce the use of PIMs, especially psychotropic drugs. They are based on different learning theories, e.g. problem-based (Roberts et al. 2001), academic detailing (Avorn et al. 1992, Wetbury et al. 2010), active educational programme (Meador et al. 1997), or individualized psychological intervention (Fossey et al. 2006). Educational programmes have also been structurated. Most of studies have focused on psychotropic use, also laxatives and NSAIDs (Roberts et al. 2001), and evidence-based medication (Crotty et al. 2004). These interventions have managed to reduce PIMs, however, other outcomes have been conflicting (Meador et al. 1997, Crotty et al. 2004, Fossey et al. 2006, Westbury et al. 2010). Only very recent trials have managed to decrease falls (Frankenthal et al. 2014), use of health services, or delirium (García-Gollarte et al. 2014).

3 Aims of the study

The aim of these studies was to explore the use of potentially harmful medications (PHMs) among older residents in assisted living facilities in Helsinki, Finland and in nursing homes in Kouvola, Finland and to investigate in a randomized controlled trial (RCT) the effects of staff training on the use of PHMs and its outcomes in these settings.

Specific aims were as follows:

1. to determine the burden and overlapping of PHMs among older people in assisted living facilities in Helsinki and in nursing homes in Kouvola (Study 1)
2. to evaluate the association of burden of PHMs on residents' health-related quality of life (HRQoL), psychological well-being (PWB), and 3-year mortality (Study 1)
3. to describe the feasibility of an educational intervention in institutional settings (Study 2)
4. to evaluate the effect of an educational intervention on the use of PHMs among older people in assisted living facilities during a 12-month follow-up with an RCT design (Study 3)
5. to investigate the effects of an educational intervention on HRQoL, hospitalizations, and mortality of participants during a 12-month follow-up with an RCT design (Study 3)
6. to evaluate the effect of an educational intervention on residents' falls and cognition during a 12-month follow-up with an RCT design (Study 4)

4 Methods

4.1 Participants and setting

Participants were recruited among residents aged ≥65 years in assisted living facilities in Helsinki (Studies 1-4) and in nursing homes in Kouvola (Study 1). Residents and their closest proxies were approached personally, one by one. They received information about the study and gave written informed consent to participate. If there was evidence of a participant's significant cognitive decline (MMSE<20), her or his closest proxy (relative or spouse) gave written consent to participate before any study procedures were initiated. Significant cognitive decline was defined at MMSE<20 in the study protocol (Pitkälä et al. 2012).

There were five inclusion criteria to participate in the study:
1. Age ≥65 years and living permanently in assisted living facilities in Helsinki or in a nursing home in Kouvola
2. Native Finnish speaking
3. Using ≥ one drug
4. Having estimated survival ≥ 6 months
5. Voluntary participation, written informed consent to participate in the study was given by the participant or her or his closest proxy in the case of the participant's MMSE<20

In 2011, there were 36 units of assisted living facilities in Helsinki housing altogether 1378 residents. Of these, 7 units with 20 wards and 320 residents were selected, and 227 residents consented to participate in the study. From the Kouvola nursing homes containing 106 residents, 99 residents chose to participate in the study. Those who did not participate either refused or were unavailable. Study 1 included participants from both Helsinki assisted living facilities and Kouvola nursing homes, whereas Studies 2, 3, and 4 comprise only participants from Helsinki assisted living facilities. All participants were examined with same measurements at the same time.

Table 11 summarizes characteristics and medication of the participants at baseline.

Table 11. Characteristics and medication of participants at baseline.

	Intervention group, N=118	Control group, N=109	Kouvola group, N=99
Age, mean (SD)	83 (8)	84 (7)	84 (7)
Females, %	65	77	68
Education <8 years, %	60	62	80
MMSE, mean (SD)	8.8 (8.2)	10.0 (8.2)	9.6 (7.8)
Charlson comorbidity index, mean (SD)	3.2 (2.0)	2.5 (1.8)	2.2 (1.4)
Mean number of regular drugs (SD)	7.5 (2.8)	7.8 (3.1)	7.3 (3.1)
Mean number of pro re nata drugs (SD)	3.6 (2.3)	2.9 (2.0)	2.5 (1.3)
Mean number of harmful drugs (SD)	2.9 (1.8)	2.5 (1.7)	2.9 (1.8)
Proportion using Beers' drugs 2003, %	25	19	58
Proportion using anticholinergic drugs, %	78	66	57
Proportion using >2 psychotropic drugs, %	34	35	31

SD = standard deviation; MMSE = Mini Mental State Examination (Folstein et al. 1975); Charlson comorbidity index (Charlson et al. 1987; Beers' drugs (Fick et al. 2003).

Participants' mean age ranged from 83 (intervention group) to 84 years (Kouvola). The proportion of females varied from 65% (intervention group) to 77% (control group). Of Kouvola nursing home residents, 80% had an education < 8 years; the corresponding proportion of Helsinki assisted living facilities residents was 60-62%. MMSE was quite low in all groups, ranging from 8.8 to 10.0. Participants had a high number of serious comorbidities according to the Charlson comorbidity index (Charlson et al. 1987), which ranged from 2.2 to 3.2, the highest being in the intervention group. The Charlson comorbidity index takes into account both number and severity of comorbidities and their association with survival. Participants regularly used more than 7 drugs on average. The mean number of pro re nata drugs varied from 2.5 to 3.6. The mean number of PHMs

was 2.5 in the control group and 2.9 in the intervention and Kouvola groups. The proportion using Beers' drugs 2003 was 19% in the control group, 25% in the intervention group, and 58% in the Kouvola group. The proportion using anticholinergic drugs varied from 57% (Kouvola group) to 78% (intervention group). The proportion using >2 psychotropic drugs concomitantly ranged from 31% to 35%.

Altogether 227 subjects from Helsinki participated in the RCT. Of these, 41 were lost during the 6-month follow-up (26 from the intervention group and 15 from the control group). Of the 41 subjects lost, 38 were deceased and one intervention participant and two control participants were lost to follow-up due to admission to hospital. During the 12-month follow-up altogether 63 participants died (39 in the intervention group and 24 in the control group). For the Kouvola group, only baseline data are used in Study 1.

4.2 Study design and randomization

Study 1 had a cross-sectional design with a 3-year follow-up for mortality.

Studies 2, 3, and 4 were based on a randomized controlled intervention trial (RCT) performed at Helsinki assisted living facilities. The RCT protocol was registered in the Australian New Zealand Clinical Trials Registry (ACTRN) under registration number ACTRN12611001078943. To avoid contamination of the intervention, units were randomized instead of individual participants. Thus, a cluster randomization was used. All 36 units in Helsinki were assessed and participating wards were selected by using the Minimum Data Set (MDS)/Resident Assessment Instrument (RAI) version 2.0 for home care (Morris et al. 2000). This was done to ensure that participating wards in the intervention and control arms had as similar as possible case-mix (psychogeriatric impairment, physical disability, or cognitive impairment).

Once the case-mix according to the MDS of each participating ward was clarified, the wards were paired into 10 dyads with similar characteristics. There were altogether 320 residents in these selected wards in Helsinki. Of these 320 residents, 93 refused or did not fulfil the inclusion criteria. Therefore, 227 residents were included in the study. Baseline assessment was performed after written informed consent to participate was received.

Computer-generated random numbers were used to randomize units into intervention arm or control arm. Altogether 118 subjects participated in the intervention group and 109 subjects in the control group.

The intervention consisted of two half-day training sessions for staff on potentially harmful drugs in older people. The residents were assessed at 6 months and 12 months.

The research process is described in the flow chart below (Figure 1).

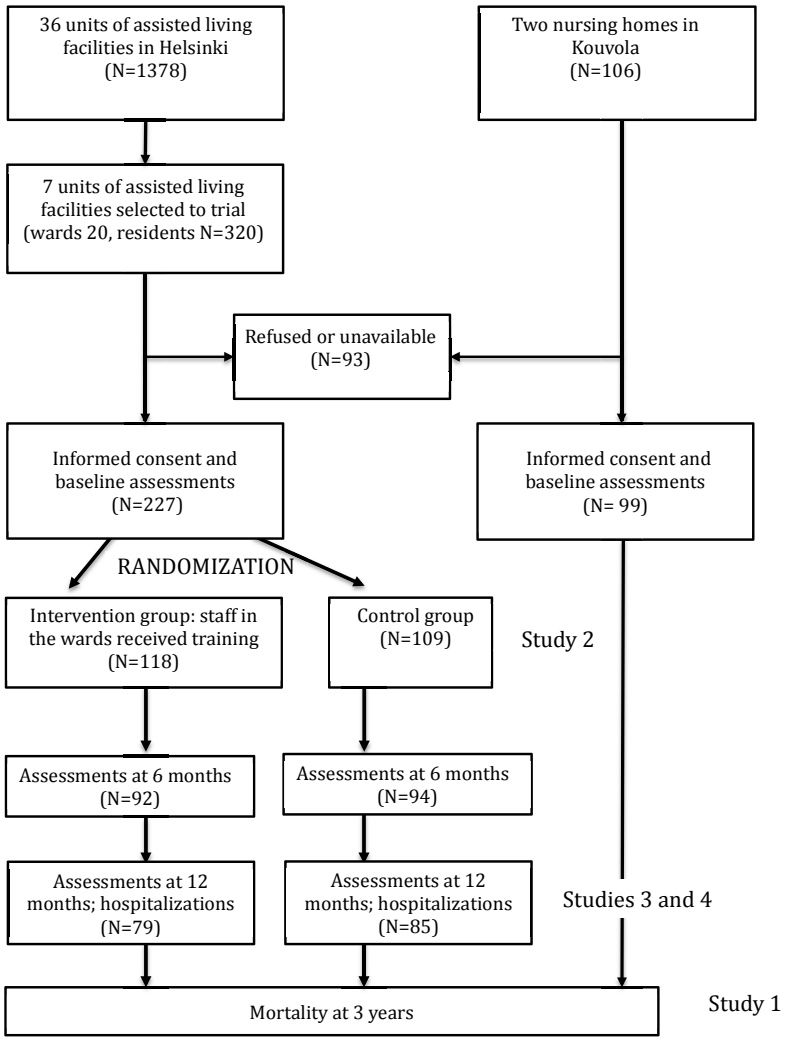

Figure 1. Flow chart of the studies

4.3 Measurements

Trained study nurses assessed residents three times: at baseline, at 6 months, and at 12 months. Study nurses were independent of the study intervention and unaware of the randomization procedures. Assessments were performed with the same procedures and at the same time in Helsinki and Kouvola.

The baseline visit lasted about one hour. The participant's demographic data were retrieved from medical records and from the closest proxies; these data included age, gender, and education defined as: 1 = primary school or less, 2 = vocational school, 3 = middle school, 4 = upper secondary school, 5 = technical college, 6 = university. Education was dichotomized in further analyses as less than 8 years (=primary school or less) and as 8 years or more.

Residents' diagnoses were retrieved from medical records, and comorbidity for each resident was calculated using the Charlson comorbidity index (Charlson et al. 1987), which is a validated and widely used measure of comorbidity among older people in institutional care (Buntinx et al. 2002). The Charlson comorbidity index is a weighted measure that takes into account both the number and seriousness of conditions. It has been shown to be a predictor of short-term mortality (Charlson et al. 1987). Residents rated their own health as healthy, quite healthy, quite unhealthy, or unhealthy. In the analyses of Study 1, self-rated health was categorized as healthy (healthy, quite healthy) or unhealthy (quite unhealthy, unhealthy).

All medications of participants, both regularly and pro re nata used, were retrieved from participants' medical records as a point of prevalence on the day of assessment. The Anatomical Therapeutic Chemical (ATC) classification system recommended by the World Health Organization (WHO 2012) was used to classify medications. The following medications were defined as potentially harmful medications (PHMs): (1) Beers' potentially inappropriate drugs 2003, (2) Drugs with anticholinergic properties (DAPs), (3) Use of >2 psychotropics concomitantly, (4) Proton Pump Inhibitors (PPIs), and (5) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). NSAIDs included both selective and non-selective NSAIDs, because also coxib use was a predictor of mortality among people aged >65 years with gastrointestinal or cardiovascular events (Abraham et al. 2008). Low-dose acetylsalicylic acid (< 250 mg) was not included in its use as antithrombotic therapy (You et al. 2012), and topically used NSAIDs were also excluded. Moreover, Beers' 2012 list includes only oral NSAIDs (AGS 2012). The proportion of users and number of PHMs per participant were determined.

PHMs and their definitions are presented in Table 12.

Table 12. Potentially harmful medications and their definitions

Medications	ATC code	Definition	Comments
Beers' PIDs 2003		Fick et al. 2003	Drugs available in Finland in 2011 presented in Appendix 2
DAPs		Fick et al. 2003, Rudolph et al. 2008, Socialstyrelsen 2010,	Drugs presented in Appendix 3
Concomitant use of >2 psychotropic drugs Psychotropic drugs included Antipsychotic drugs Antidepressants Anxiolytics Hypnotics	 N05A N06A N05B N05C	Socialstyrelsen 2010	Drugs presented in Appendix 4
PPIs	A02BC	Teramura-Grönblad et al. 2010	Drugs presented in Appendix 4
NSAIDs	M01A	Socialstyrelsen 2010	Low-dose acetylsalicylic acid (<250 mg) and topically used NSAIDs were exluded. Drugs presented in Appendix 4

ATC= Anatomical Therapeutic Chemical classification; DAPs=Drugs with Anticholinergic Properties; NSAID=Non-Steroidal Anti-Inflammatotory Drug; PID=Potentially Inappropriate Drug; PPI=Proton Pump Inhibitor

Nutritional status was measured using the Mini Nutritional Assessment (MNA) (Guigoz et al. 2002). The MNA is a reliable and validated instrument to examine the nutritional status of older people. The MNA score varies from 0 to 30, an MNA score <17 indicates malnourishment, 17 to 23.5 indicates the risk of malnourishment, and >23.5 indicates good nutritional status (Appendix 5).

Cognition was assessed by using the Mini Mental State Examination (MMSE) (Folstein et al. 1975), verbal fluency (Morris et al. 1989, Morris et al. 1993), and the clock drawing test (Morris et al. 1989, Morris et al. 1993). MMSE is the most widely used test measuring cognition of older people. MMSE is presented in Appendix 6. Verbal fluency is a part of CERAD (Morris et al. 1989). In verbal fluency, the participant names as many animals as possible within one minute; the cut-off point for normal is ≥16 (Hänninen et al. 2010). The Clock Drawing Test is a simple measure of visuospatial ability (Sunderland et al. 1989). The face of a clock with 12 numbers and clock hands is drawn with the time reading 11:10. The task is graded from 0 to 6; a result <5 is considered abnormal (Hänninen et al. 2010). The residents' stage of dementia was assessed using the Clinical Dementia Rating (CDR) scale (Hughes et al. 1982). The CDR score also includes estimations of cognitive, social, and physical functioning. There are six domains to assess cognition and function: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and

personal care (Hughes et al. 1982). Each domain is given a rating of 0, 0.5, 1, 2, or 3. When the final score is determined, the memory domain may increase or decrease the overall rating by 1. CDR score 0 means no dementia, 0.5 possible or very mild dementia, 1 mild dementia, 2 moderate dementia, and 3 severe dementia (Hughes et al. 1982). CDR, clock drawing test, and verbal fluency are presented in Appendix 7.

Quality of life was measured by using the 15D health-related quality of life scale (15D HRQoL) (Sintonen 2001). The 15D HRQoL is a generic, validated, and self-administered measure of HRQoL with scores ranging from 0 (poorest) to 1 (excellent) (Sintonen 2001). If the person is physically or mentally unable to reply, proxy administration can also be used (Sintonen 2001). The 15D includes 15 domains related to mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. 15D is widely used and available in several languages (Sintonen 2001). 15D includes an item on mobility, which was used in Study 4 as a covariate for falls. The participant was considered as dependent in mobility if she/he needed help to move around indoors or was totally inmobile.

Psychological well-being was assessed using the psychological well-being (PWB) scale (Routasalo et al. 2009). The PWB scale includes six items: life satisfaction (yes/no), feeling useful (yes/no), having plans for the future (yes/no), having zest for life (yes/no), feeling depressed (seldom or never/sometimes/often or always), and loneliness (seldom or never/sometimes/often or always) (Routasalo et al. 2009). The PWB score was calculated by summing the scores for each item and dividing by the number of items completed by the participant. Score 0 represents the poorest and score 1 the best PWB. The content of questions of PWB have good reliability and criterion validity, as its items represent areas considered important in psychological well-being in World Health Organization Quality of Life Instruments (WHOQOL-BREF) (Routasalo et al. 2009). It has also prognostic validity in survival (Pitkälä et al. 2004b). The PWB scale is presented in Appendix 8.

The 6- and 12-month assessments included MMSE, verbal fluency, clock drawing test, 15D HRQoL, PWB scale, and drug use.

Information on falls was retrieved from the nurse's daily entries during the 12-month follow-up. At 12 months, data on the use of health and social services were retrieved from patients' medical records and and mortality data from the Population Register Centre of Finland.

In Study 1, data on mortality during the 3-year follow-up were obtained from from Population Register Centre of Finland.

Table 13 describes the timeline of all assessments.

Table 13. Timeline of study assessments

Assessment	Comparability of wards; interviews	Baseline assessment	6-month assessment	12-month assessment	3-year assessment
Inclusion criteria, informed consent	+				
Demographics		+			
CDR		+			
MNA		+			
Diagnoses		+			
Medication		+	+	+	
MMSE		+	+	+	
Verbal fluency		+	+	+	
Clock drawing test		+	+	+	
15D HRQoL		+	+	+	
PWB		+	+	+	
Falls			+	+	
Hospitalization and use of health services				+	
Mortality				+	+

CDR=Clinical Dementia Rating; MMSE=Mini Mental State Examination; MNA=Mini Nutritional Assessment; PWB=Psychological Well-Being; 15D HRQoL=15 Dimensional Health-Related Quality of Life

4.4 Intervention

The intervention was an educational intervention using problem-based learning methods and a learner-centred approach. After RAI assessments, the selected dyads were randomly divided into two groups, the intervention and the control arms. The nursing staff of the intervention arms received education on two afternoons by three geriatricians. Also consulting physicians were welcomed to educational sessions. The intervention arm included 10 wards. There were altogether 17 registered nurses and three consulting physicians. One of the physicians was a geriatrician, and he participated in one of the training sessions. One of the two primary care physicians also participated in one session.

Contents of the first 4-hour session included polypharmacy, changes in drug metabolism in older age, especially renal failure and use of Renbase (Renbase 2011), common drug-drug interactions

and use of the SFINX database (SFINX 2011), and potentially harmful drugs (psychotropic drugs, Beers' criteria drugs, drugs with anticholinergic properties, NSAIDs, and PPIs) and their adverse effects. Also discussed were potentially beneficial drugs, such as vitamin D (Bischoff-Ferrari et al. 2009) and anticoagulation in case of atrial fibrillation (You et al. 2012), for institutionalized older people.

Renbase is a database of information on the pharmacokinetics and safety of various drugs in renal failure. It gives dosage recommendations for 1500 drugs. The SFINX (Swedish, Finnish, Interaction, X-referencing) database is a drug-drug interaction database containing information on the consequences of and recommendations for about 18 000 drug-drug interactions.

The second 4-hour session was a case-based and problem-oriented learning workshop. Each ward brought 2-3 of their own patient cases with various drug problems, and participants were encouraged to discuss in groups and to present cases to their peers. Participants were advised to explore the medication lists of the residents in their wards and to discuss these drug problems subsequently with their consulting physicians to improve their patients' care. Each participant also received a 2-page list of harmful drugs to identify them in practice. Nursing staff in all wards of the nursing homes in Kouvola received this training. Nursing staff in the control wards in Helsinki received similar training after a 12-month follow-up.

4.5 Outcome measures

The primary outcome measures were the proportion of persons using PHMs (Beers' drugs, DAPs, >2 psychotropics, NSAIDs, and PPIs) in Studies 2-4 and change in the number of PHMs in Studies 3 and 4.

Secondary outcome measures were change in the health-related quality of life according to the 15D HRQoL (Sintonen 2001) in Study 3 and changes in cognition measured by clock drawing test (Sunderland et al. 1989) and verbal fluency (Morris et al. 1989) during the 12-month follow-up in Study 4. Number of falls and fallers were retrieved from patients' records in Study 4. Recording falls is part of nursing staff routine care procedures, and this information may be considered reliable. The use of health care services – mainly hospitalizations – during the 12-month follow-up was retrieved from medical records in Study 3. Mortality up to 12 months was compared between the intervention and control arms in Study 3. In Study 1, mortality data were retrieved from the Population Register Centre at the end of the 3-year follow-up.

4.6 Statistical analyses

Sample size calculation in the RCT was based on the change in the prevalence of potentially harmful medication use. The required sample size was calculated assuming that 36% of the control group use inappropriate drugs (Raivio et al. 2006), aiming at a minimum group difference of 20% after the intervention, with type I error 5% and power 80%. These assumptions resulted in 106 participants per group.

In the baseline findings of the RCT (Studies 2,3, and 4), the categorical variables (e.g. gender, education, diagnoses) were described as proportions (%) and analysed by X^2 or Fischer's exact test when appropriate. The continuous variables (e.g. age, PWB) were presented using means with standard deviations (SD) or ranges. For variables with normal distribution, statistical comparisons between the groups were performed using Student's *t* test. For non-normally distributed continuous variables, statistical comparison between the groups was performed using the Mann-Whitney U test. The normality of the variables was tested with the Shapiro-Wilk W-test.

All residents assessed at baseline and at least once during the two follow-ups were included when analysing changes in the use of medications and HRQoL in Study 3 and when analysing changes in the cognitive measures in Study 4 (modified intention-to-treat analyses). All randomized residents were included when analysing use of health services and mortality in Study 3 and when analysing the number and rate of falls in Study 4 (intention-to-treat analyses).

In Studies 3 and 4, repeated measures were analysed using generalized estimating equation (GEE) models, with appropriate distribution and link functions, and an unstructured correlation structure, with treatment groups, time, and their interaction as fixed factors. GEE models were developed as an extension of general linear models (e.g. ordinary least squares (OLS) regression analysis) for analysis of longitudinal and other correlated data. The GEE models took into account the correlation between repeated measurements for the same participant. These models do not require complete data for all participants at all time points. Incidence rate ratios (IRRs) for hospital days and ambulatory services in Study 3 and for falls in Study 4 were estimated and compared between the groups using the Poisson regression models with robust standard error. Cox proportional hazard model was used to test the effect of intervention on mortality. Analyses were adjusted for age, sex, and comorbidities and in the falls analysis also for mobility. Confidence intervals (95%) were calculated for the most important outcomes.

In Study 1, clinical and demographic characteristics of residents in four PHM burden groups (G) (G0=no PHMs, G1=PHMs according to one criterion, G2=PHMs according to two criteria, G3=PHMs according to three criteria) (Beers' 2003, DAPs, or >2 psychotropics concomitamtly) were compared. The statistical hypothesis of linearity was evaluated using analysis of variance (ANOVA), Cochran-Armitage test, and logistic models. In case of violation of the assumptions (non-normality), a bootstrap-type test was used. The relationship between group allocation and each of the main outcomes was analysed with multivariate forward stepwise continuation-ratio logistic regression for ordered response data.

P-values <0.05 were considered statistically significant.

Analyses were performed using STATA software (version 14.0) (StataCorp LP, College Station, TX, USA).

4.7 Ethical considerations

The Ethics Committee of Helsinki University Central Hospital approved the study protocol. Participants and their closest proxies received information about the study and its content and purpose, and each participant or her/his closest proxy gave written informed consent to participate before any study procedures commenced.

5 Results

Baseline findings are presented in the Methods section.

5.1 Burden of PHMs (Study 1)

Study 1 examined the overlap and burden of potentially harmful medications (Figure 2). PHM was defined as use of any of the following: Beers' 2003 drugs, DAPs, or >2 psychotropics.
Of all 326 participants, 221 used DAPs; 93 used only DAPs as PHM, 57 used concomitantly >2 psychotropic drugs, but not Beers' drugs, and 30 used concomitantly Beers' 2003 PIDs but not >2 psychotropic drugs. Of all participants, 105 used concomitantly >2 psychotropic drugs; 2 had only excess psychotropic use as PHM, and 5 used also Beers' 2003 PIDs. Of all participants, 105 used Beers' 2003 PIDs; 29 had only Beers' 2003 PIDs as PHM. Of all participants, 30 used DAPs and Beers' drugs simultaneously. Altogether 41 of all 362 participants used PHM according to all three criteria, and 69 did not use medication according to any of these three criteria.

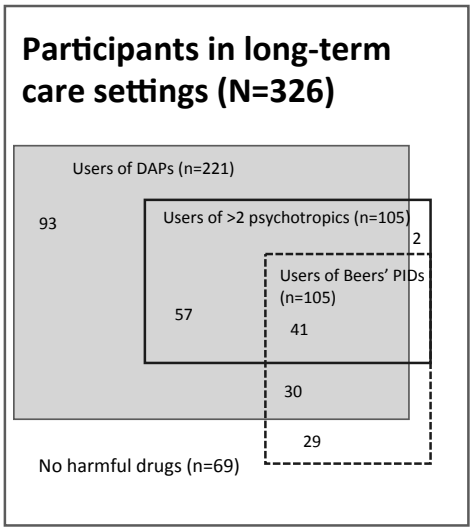

Figure 2. Overlapping and burden of potentially harmful medication. Harmful medication: participants using at least one drug with anticholinergic properties, or >2 psychotropic drugs concomitantly, or at least one Beers' 2003 PID

In Study 1, participants in the Helsinki assisted living facility and Kouvola nursing homes were divided into four groups according to their use of PHMs. Participants in Group 0 (G0)(n=69) did not use any PHMs according to the three criteria of Beers' 2003 potentially inappropriate drugs, DAPs, or concomitant use of >2 psychotropic drugs. Participants in Group 1 (G1)(n=124) used PHMs according to one criterion, participants in Group 2 (G2)(n=92) used PHMs according to two criteria, and participants in Group 3 (G3)(n=41) used PHMs according to all three criteria. When

calculating the total number of PHMs, each PHM was counted only once even if it was included in several definitions.

Medication use and characteristics in the four groups are summarized in Table 14. There were significant differences in characteristics and medication use between the groups. The mean number of regular drugs ranged from 6.5 to 9.7; the number of drugs increased stepwise as more PHM criteria were fulfilled. The same significant difference was seen in the mean number of PHDs, increasing from 0.8 to 4.8, as well as in the mean number of Beers' drugs, DAPs, and psychotropic drugs. Participants who used PHMs from all three categories were younger. However, there were no significant differences in gender, Charlson's comorbidity index, or MMSE between the groups.

Table 14. Characteristics and use of medications among groups according to fulfilling 0-3 criteria for potentially harmful medications (PHMs).

Characteristics	G0, N=69	G1, N=124	G2, N=92	G3, N=41	p-value[1]
Age, mean±SD	85.9±7.5	83.8±6.9	82.4±7.3	81.4±6.7	<0.001
Gender: female, %	66.7	74.2	72.8	56.1	0.41
Charlson comorbidity index[2], mean±SD	2.4 ± 1.7	2.7±1.8	2.5±1.5	3.0±1.8	0.31
MMSE[3], mean±SD	8.7±6.5	9.1± 8.4	9.7±8.3	11.1±9.0	0.13
Number of regular drugs, mean±SD	6.5±2.9	6.8±2.8	8.4±2.8	9.7±2.6	<0.001
Number of potentially harmful drugs[4], mean±SD	0.8±0.7	2.0±0.9	3.6±1.2	4.8±1.2	<0.001
Beers' drugs, mean±SD	0±0.0	0.3±0.5	0.5±0.7	1.5±0.7	<0.001
Drugs with anticholinergic properties[5], mean±SD	0±0.0	0.9±0.7	1.5±0.9	2.0±0.8	<0.001
Psychotropic drugs, mean±SD	0.8±0.7	1.4±0.8	2.9±1.1	3.9±1.0	<0.001
Self-rated health good, %	86.2	70.8	65.3	66.7	0.015
PWB[6], mean±SD	0.74±0.18 (n = 60)	0.68±0.23 (n = 104)	0.67±0.23 (n = 81)	0.61±0.25 (n = 37)	0.0044
15D[7], mean±SD	0.64±0.11	0.60±0.12	0.60±0.13	0.59±0.12	0.022

G0=participants not fulfilling any of the PHM criteria (Beers' PIDs, DAPs, or use of >2 psychotropics concomitantly); G1=participants fulfilling 1 criterion; G2=participants fulfilling 2 criteria; G3=participants fulfilling 3 criteria; [1]Differences between the groups were evaluated using analysis of variance (ANOVA), Cochran-Armitage test, or logistic models. In case of violation of assumptions (non-normality), a bootstrap-type test was used. No adjustments were made in these analyses; [2]Charlson et al. 1987; [3] Folstein et al. 1975; [4]Included Beers' 2003 drugs, anticholinergic drugs, and psychotropic drugs; [5] Fick et al. 2003, Rudolph et al. 2008, Socialstyrelsen 2010; [6]Routasalo et al. 2009; n = number of responders in this item; [7]Sintonen 2001

5.1.1 Predictors of burden of PHMs and associations with participants' quality of life and mortality

In forward stepwise ordered (continuation-ratio) logistic regression for burden of PHMs (by 4 classes from G0 to G3), younger age (OR) 0.94, 95% CI 0.90 to 0.99; p=0.014], lower HRQoL according to 15D (0.57 per SD, 95% CI 0.39 to 0.85; p=0.006), and higher MMSE (1.06, CI 1.01 to 1.11; p=0.028) were associated with higher burden of PHMs.

Burden of PHMs was associated with lower scores in HRQoL according to 15D, in PWB, and in self-rated health. 15D was 0.64 in G0, 0.60 in G1, 0.60 in G2, and 0.59 in G3 (p=0.0031, adjusted for age, gender, and comorbidity). The respective figures in PWB were 0.74, 0.68, 0.67, and 0.61 (p=0.0041, adjusted for age, gender, and comorbidity). In G0, 86% of participants felt healthy, the respective figures being in G1 71%, G2 65%, and G3 67% (p=0.020, adjusted for age, gender, and comorbidity). In PWB and self-rated health, a number of participants with low cognition were unable to answer. Only responders' answers were analysed. If a person is unable to reply, proxy administration can also be used with 15D HRQoL (Sintonen 2001).

Data on mortality over the 3-year follow-up were obtained from the Population Register Centre. The proportion of participants deceased was 64% in the group in which residents did not use PHMs according to any PHM criteria, 62% in the group where residents used PHMs according to one criterion, 48% in the group where residents used PHMs according to two criteria, and 51% in the group where residents used PHMs according to three criteria. No differences in mortality emerged between the groups according to burden of PHMs when adjusted for age and gender (p=0.10).

5.2 Educational intervention to reduce PHM use among residents in assisted living facilities

5.2.1 Baseline findings and feasibility (Study 2)

Characteristics and medications of participants at baseline are described in Table 11. At baseline, no significant differences were present between the intervention and control arms in mean age, education, or cognition. Participants in the intervention group had more comorbidities than participants in the control group (p<0.004). The proportion of females tended to be lower in the intervention group than in the control group (p=0.050). No significant difference emerged in the mean number of regular drugs between the groups (p=0.79). However, in the intervention group the

mean number of pro re nata drugs was significantly higher than in the control group, 3.6±2.3 versus 2.9±2.0 (p=0.007). There was also a significant difference in the proportion of subjects using harmful medications, 83% versus 72%, respectively (p=0.038). However, there was no significant difference in the mean number of harmful drugs, 2.9±1.8 versus 2.5±2 (p=0.28). Nor were there significant differences in the proportion of subjects using Beers' 2003 PIDs, 25% versus 19% (p=0.25), the proportion using DAPs, 78% versus 66% (p=0.089), or the proportion using >2 psychotropic drugs concomitantly, 34% versus 35% (p=0.30).

Feasibility

Three units were randomized into the intervention arm with three wards in two units and four wards in one unit. Table 15 describes the number of registered nurses in the wards and how they participated in the educational sessions. In 7 of the 10 wards, nurses participated in both training sessions. There were also two wards in which the nurses did not participate in the first session, but participated in the second session. Unfortunately, in one ward the nurses did not participate in either of the sessions. Instead, they received tailored individual training. In addition, there were three treating physicians in the intervention wards: one geriatrician and two primary care physicians. The geriatrician and one of the primary care physicians participated in one afternoon session.

Table 15. Participation in intervention training sessions.

Unit (U)	Wards, n	Registered nurses, n	Sessions, nurses, n	Sessions, physicians, n
U 1	3	5	6	1(GP)
U 2	3	5	5	0 (GP)
U 3	4	7	6	1 (geriatrician)

GP= general practioner

5.2.2 Effect of intervention on use of PHMs (Study 3)

Over the 12-month follow-up period, the prevalence of PHMs decreased significantly in the intervention group (-11.7%, 95% CI -20.5 to -2.9; p=0.009). No significant change occurred in the control group (+3.4%, 95% CI -3.7 to 10.6; p=0.34). There was a significant difference in change in the prevalence of the use of PHMs between the groups at 12 months (p=0.022, adjusted for age, sex, and comorbidities). The mean number of harmful drugs decreased in the intervention group (-

0.43, 95% CI -0.71 to -0.15; p= 0.0024), whereas in the control group it remained stable (+0.11, 95% CI -0.09 to +0.31; p= 0.27). The difference in change in the mean number of PHMs between the groups was significant (p=0.0035, adjusted for age, sex, and comorbidities) (see Figure 3).

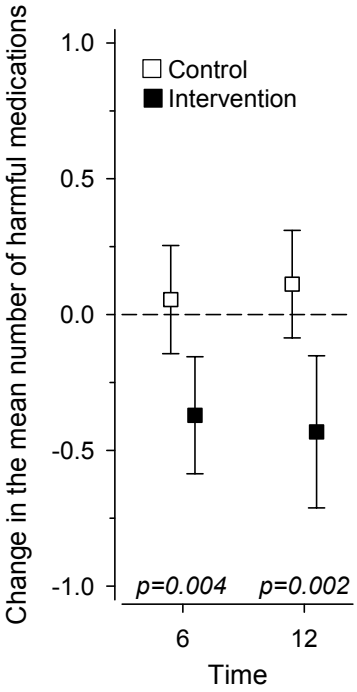

Figure 3. Change from baseline in the mean number of potentially harmful medications at 6 months and 12 months. P-values between the groups are adjusted for age, sex, and comorbidities.

When the PHMs were examined separately, the use of psychotropic drugs decreased significantly in the intervention group compared with the control group (p=0.022, adjusted for age, sex, and comorbidities). The decrease in the number of Beers' drugs (p=0.23) and DAPs (p=0.17) in the intervention group was not significant. The results are illustrated in Figure 4.

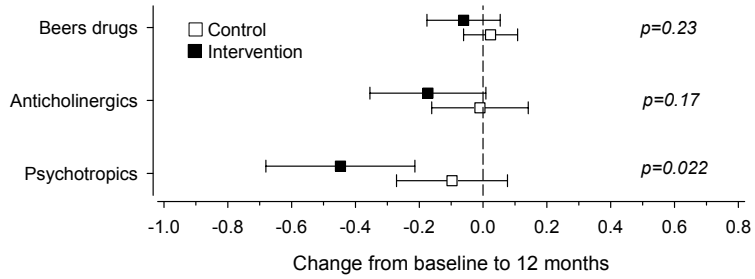

Figure 4. Change from the baseline in the mean number of Beers' potentially inappropriate drugs, drugs with anticholinergic properties, and psychotropic drugs.

5.2.3 Effect of intervention on participants' quality of life (Study 3)

Participants' quality of life was measured at baseline, 6 months, and 12 months using the 15D Health-Related Quality of Life (15D HRQoL) scale.

When the effect of the intervention on the quality of life was assessed, HRQoL declined significantly more slowly in the intervention group (-0.038; 95% CI -0.054 to -0.022) than in the control group (-0.072, 95% CI -0.089 to -0.055; p=0.005, adjusted for age, sex, and comorbidities). Breathing, sleeping, and speech were the dimensions of 15D that benefited most in the intervention group (Figure 5).

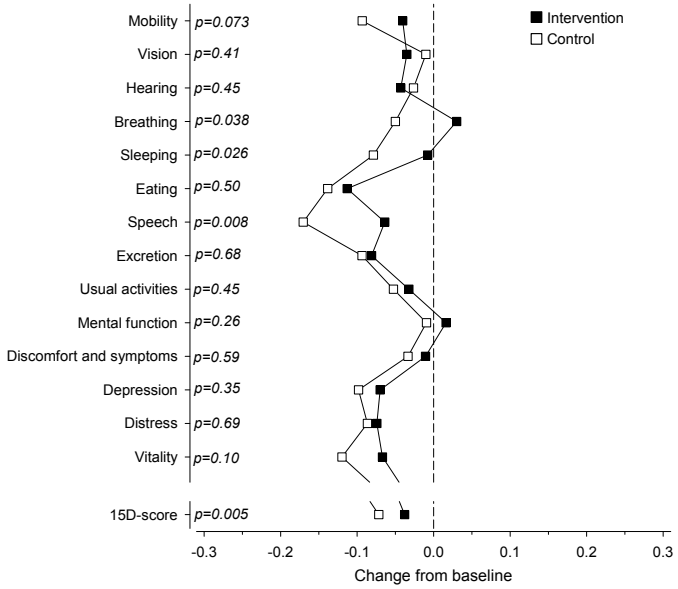

Figure 5. Changes from baseline in 15D HRQoL dimensions.

5.2.4 Effect of intervention on participants' hospitalization and use of health services (Study 3)

A significant difference was present in the use of hospital days between the intervention and control groups. Residents in the intervention group used less hospital days, 1.4/person/year (95% CI 1.2 to 1.6), whereas the respective figure in the control group was higher, 2.3/person/year (95% CI 2.1 to 2.7) (IRR 0.60, 95% CI 0.49 to 0.75; p <0.001, adjusted for age, sex, and comorbidities). There was no significant difference in the use of ambulatory services between the groups: in the intervention group 0.7/person/year (95% CI 0.5 to 0.8) and in the control group 0.6/person/year (95% CI 0.5 to 0.8) (IRR 0.98 (95% CI 0.69 to 1.39); p=0.92, adjusted for age, sex, and comorbidities).

5.2.5 Effects of intervention on participants' mortality (Study 3)

Mortality was investigated over the one-year follow-up. At 12 months, 33% of the participants in the intervention group were deceased, and the respective figure in the control group was 22% (unadjusted p=0.064). When adjusted for age, sex, and comorbidities in the Cox proportional hazard model, no significant difference in mortality was present between the intervention and control groups (HR 1.04, 95% CI 0.79 to 1.36; p=0.79).

5.2.6 Effect of intervention on participants' falls (Study 4)

Data on falls were retrieved from each participant's medical records. There were significantly less falls in the intervention group (n=171 falls; 2.25 falls/person/year, 95% CI 1.93 to 2.62) than in the control group (n=259 falls; 3.25 falls/person/year, 95% CI 2.87 to 3.67). The age-, sex-, and comorbidity-adjusted IRR for falls in the intervention wards was 0.72, 95% CI 0.59 to 0.88; p <0.001. When adjusted for age, sex, and mobility, the respective IRR was 0.80, 95% CI 0.66 to 0.97; p=0.025. There were 42 fallers in the intervention group, 27 falling more than once during the 12-month follow-up, and 60 fallers in the control group (p=0.0032). Altogether, 41 individuals fell more than once. Four residents in the control group fell between 20 and 22 times each and in the intervention group three residents fell 28 times each. When the residents were stratified according to their baseline MMSE, the residents with MMSE scores ≥10 points benefited from the intervention with respect to falls. There were no differences between the intervention and control

groups in residents with MMSE <10 (see Figure 6). The number of participants in different MMSE groups is presented in Table 16.

Table 16. Number of participants in different MMSE (Mini Mental State Examination) groups

Group	MMSE <10	MMSE 10-15	MMSE >15
Intervention	45	23	25
Control	50	22	24
All	95	45	49

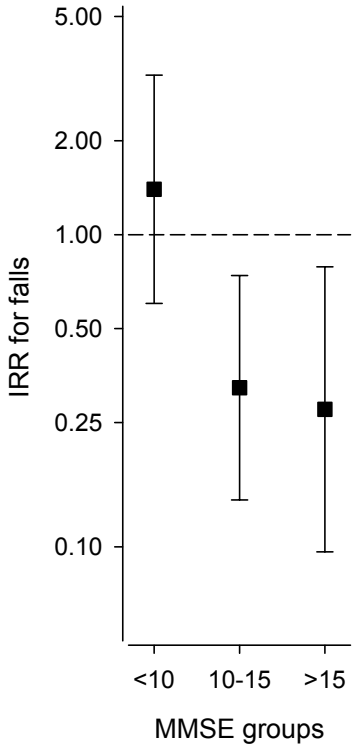

Figure 6. IRR (Incident Risk Ratio) for falls stratified to according to participants' baseline MMSE. MMSE= Mini Mental State Examination (Folstein et al. 1975)

5.2.7 Effect of intervention on participants' cognition (Study 4)

Cognition was assessed using verbal fluency (Morris et al. 1989) and clock drawing test (Morris et al. 1989) at baseline, 6 months, and 12 months. There were no significant differences in changes in

verbal fluency or clock drawing test between the intervention and control groups at 6 months or 12 months relative to baseline (see Figures 7 and 8). Results were adjusted for age, sex, and comorbidities.

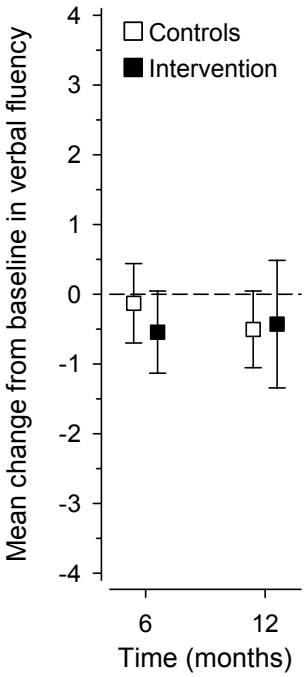

Figure 7.
Changes in cognition in the intervention and control groups according to verbal fluency scores (Morris et al. 1989). P=0.37 at 6 months and 0.88 at 12 months, adjusted for age, sex, and comorbidities.

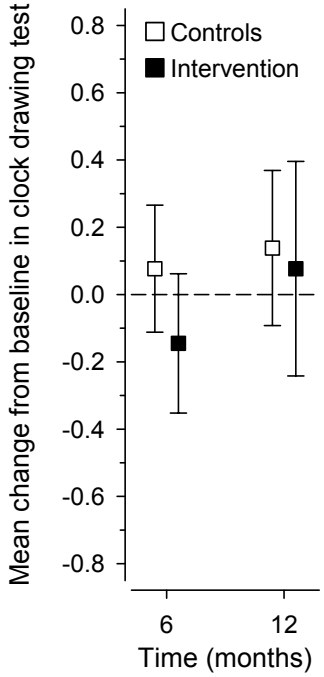

Figure 8.
Changes in cognition in the intervention and control groups according to clock drawing test (Morris et al. 1989). P=0.088 at 6 months and 0.53 at 12 months, adjusted for age, sex, and comorbidities.

6 Discussion

6.1 Main findings

There was a high burden in the use of PHMs in institutional settings. In this cross-sectional study, 13% of participants used PHMs from all three categories of PHMs (Beers' drugs, DAPs, >2 psychotropics), and 79% used PHMs from at least from one category of PHMs. Use of PHMs was associated in a stepwise manner with poorer HRQoL, PWB, and self-rated health. The use of PHMs was not associated with mortality over a 3-year follow-up.

The educational intervention in the cluster randomized controlled trial was successful in several respects. There were some differences in characteristics of the intervention and control arms at baseline, and the outcomes had to be adjusted accordingly in the final analyses. Of the participants, 83% in the intervention group and 72% in the control group were administered PHMs at baseline. The training using activating learning methods was fairly well accepted by staff.

The intervention had an effect on the use of PHMs. The mean number as well as the proportion using PHMs decreased significantly in the intervention group relative to the control group during the one-year follow-up. Of the potentially harmful drugs, the use of psychotropic drugs decreased significantly in the intervention group compared with the control group. HRQoL decreased significantly slower and the use of hospital days was significantly lower in the intervention group than in the control group.

The incidence of falls decreased significantly in the intervention group compared to the control group. The participants with MMSE>10 in the intervention group had less falls than the respective controls, whereas in participants with MMSE<10 no difference was observed between the groups. The intervention had no effect on cognition according to the verbal fluency or clock drawing test. No difference emerged in mortality between the intervention and control groups over the one-year follow-up.

6.2 Strengths and limitations of the study

This study was carefully planned and included an exploration of the use of PHMs in various institutional settings at baseline. The PHMs were defined with internationally validated criteria. The list of PHMs was a combination of several lists in order to be comprehensive. It consisted of the Beers' 2003 list (Fick et al. 2003), including those drugs available in Finland at the time of the

study, a combination of several anticholinergic lists (Fick et al. 2003, Rudolph et al. 2008, Socialstyrelsen 2010), and the concomitant use of >2 psychotropics (Socialstyrelsen 2010), PPIs (Teramura-Grönblad et al. 2010), and NSAIDs (Socialstyrelsen 2010). At the time of planning these studies, the criteria for PHMs had to be retrieved from various sources since, for example, the available Beers' criteria in 2011 (Fick et al. 2003) included only few psychotropics. Moreover, all DAPs, NSAIDs, or PPIs available in Finland were not included in the Beers' criteria. At the time of planning the study in 2010, there was an increasing number of reports of adverse events with these medications. Therefore, a novel list of PHMs was created for this study based on the literature and in agreement with the research team. In fact, the Beers' criteria (AGS 2012, AGS 2015) have evolved since 2011, and the current criteria (AGS 2015) are fairly similar to the PHM list compiled here. Medications of the participants were retrieved from medical records to ensure reliability.

The effectiveness of the educational intervention was tested in a rigorous randomized controlled trial. There were very few exclusion criteria for older participants. Sample size was calculated to ensure sufficient statistical power to detect clinically meaningful differences between the intervention and control groups. A cluster randomization design was used to avoid contamination of intervention procedures. The units were selected using Minimum Data Set (MDS)/Resident Assessment Instrument (RAI) to ensure as similar as possible patient profiles in the intervention and control arms.

The study nurses performing the assessments were experienced and well trained. They were kept unaware of the group to which units were randomized. The assessment tests used in this study are widely used and well validated. Therefore, the data collection may be considered reliable. The primary outcome measures were selected to be sensitive to change. The number of PHMs at baseline was high; therefore, there was no floor effect in reducing them. 15D HRQoL has been shown to be sensitive to change in previous Finnish studies (Pitkälä et al. 2008). It can be used even if a participant is unable to answer; in these cases, the participant's closest proxy can anwer (Sintonen 2001).

The intervention was planned to be light and easy to implement in other facilities in the future. We used activating and problem-based learning methods (Dolmans et al. 2005), which might encourage nurses to pay attention to medication problems when caring for their patients. Finally, the studies assessed important and relevant outcomes for older people such as quality of life, falls, cognition, and hospitalizations.

The studies also have several limitations. Due to cluster randomization, there were some differences at baseline in the characteristics of participants between the intervention and control groups. This was taken into account in the analyses. The results have been adjusted for age, sex, and comorbidity, and, in case of falls, also for mobility. There was a high staff turnover, and some nurses may have moved from intervention wards to control wards. This may have diluted some of the trial effects.

The population in RCT was old and had high comorbidity so there was a fairly high attrition rate, 28%, over the one-year follow-up. When analysing the changes in the use of PHMs and HRQoL, modified intention-to-treat analyses were used, i.e. all residents assessed at least at 6 months or 12 months were included. However, intention-to-treat analyses were used when analysing falls, health service utilization, and mortality, and thus, all randomized residents were included.

Many participants had severe cognitive decline. When PWB and self-related health were tested, these participants were unable to answer. Only responders' answers could be analysed.

In Study 1, medications, HRQoL, and PWB were assessed cross-sectionally. Even if we found associations between burden of PHMs and decline in HRQoL and PWB, causality in this cross-sectional study cannot be established. Participants were frail older people, and mortality and drop-out rates were high. The study was performed in two types of facilities in two communities, and the results might not be generalizable to other cultures.

6.3 Medication use (Studies 1–4)

The mean number of regularly used drugs among all participants of this study was 7.5. Therefore, a large proportion of participants had polypharmacy (Onder et al. 2012b). In Finnish studies exploring drug use in institutional settings, the number of regularly used drugs has been at a similar level (Hosia-Randell et al. 2008, Nurminen et al. 2009, Pitkälä et al. 2015). Our result also corresponds well with the findings among institutionalized older people in Europe (Onder et al. 2012b, Bourgeois et al. 2012, Johnell and Fastbom 2012) and in Australia (Stafford et al. 2011).

There are numerous criteria to recognize inappropriate drugs for older people and to improve the quality of medication (Samsa et al. 1994, Fick et al. 2003, Basger et al. 2008, Gallagher and Mahony 2008, Rognstad et al. 2009). Many of these are suitable only in their own countries and some are fairly complicated and difficult to apply in clinical practice (Spinewine et al. 2007). The

list used in this study was compiled from different sources (Fick et al. 2003, Rudolph et al. 2008, Socialstyrelsen 2010) to be as comprehensive as possible. The list was explicit. Thus, only drugs to be avoided were included in the PHMs.

The proportion of residents using PHMs was quite high, 83% in the intervention group. The proportion using Beers' inappropriate drugs varied between 19% in the control group and 58% in the Kouvola group. The proportion of those using DAPS varied from 57% in Kouvola to 78% in the intervention group, and the proportion of those using >2 psychotropics from 31% in Kouvola to 34% in the intervention group. In previous Finnish studies, about one-third of nursing home residents and acute hospital patients received Beers' potentially inappropriate drugs (Raivio et al. 2006, Hosia-Randell et al. 2008). According to studies in Europe, up to half of NH residents were on Beers' PIDs (Ruggiero et al. 2010). In USA, this proportion varied from 26% to 50% (Briesacher et al. 2005, Lau et al. 2004). The highest figures were from Brazil, 83% (Vieira de Lima et al. 2013).

The use of DAPs was quite high. In earlier Finnish studies, the proportions of elderly residents using DAPs have varied between 42% and 55% (Kumpula et al. 2011, Teramura-Grönblad et al. 2011). These two studies had used ARS score (Rudolph et al. 2008) to define DAPs. However, the present study used also DAPs from two other criteria, Beers' 2003 and Swedish quality indicator list 2010. This may in part explain the higher prevalence in the present study than in previous studies. In Sweden, the prevalence of DAPs in institutional settings was lower (12% to 21%) (Bergman et al. 2007, Olsson et al. 2010, Haasum et al. 2012). These studies used the Swedish quality indicator list, which contains less DAPs than the combination list applied here. In other countries, the prevalence has varied from 21% to 82% (Kersten et al. 2013b, Kolanowski et al. 2009). The results have depended on – besides the criteria to define DAPs – also on the characteristics of the cohorts studied.

Two-thirds of the participants used >2 psychotropics concomitantly. According to other Finnish studies, use of psychotropic drugs has been common among institutionalized older people. About 71-80% have been administered at least one psychotropic in these studies (Hosia-Randell and Pitkälä 2005, Alanen et al. 2006, Nurminen et al. 2009). In Sweden, the use of psychotropics among institutionalized older people has varied from 38% to 85% (Schmidt et al. 1998a, Holmqvist et al. 2003, Lövheim et al. 2008, Olsson et al. 2010), the lowest use being from the year 1982 (Lövheim et al. 2008). According to studies from other countries, use of psychotropics among institutionalized older people has been common; at least half of the residents have been on psychotropics (Table 8).

PPIs are one of the most frequently used medications (Forgacs and Loganayagam 2008). In our study, the proportion of PPI users was 37-42%. According to other recent Finnish studies, the proportion of PPI users has been from 22% to 24% (Teramura-Grönblad et al. 2010, Teramura-Grönblad et al. 2012). The data in the two studies by Teramura-Grönblad et al. were from 2003 and 2007, while the data in our study was from 2011; thus, based on these results the use of PPIs in Finland has increased. Of residents in US nursing homes, 27% received PPIs (Rane et al. 2017). NSAID users comprised 3.3% in the intervention group and 5.5% in the control group. These proportions are similar to those in Norwegian NHs (Sandvik et al. 2016).

6.4 Burden of PHMs (Study 1)

The burden of PHMs was high among residents in assisted living facilities and nursing homes. More than three in four residents used PHMs according to at least one of the three criteria: Beers' PIDs 2003, DAPs, or concomitant use of >2 psychotropic drugs. To our knowledge, few studies have simultaneously investigated PHMs according to various criteria. The use of PHMs according to multiple definitions was associated with lower health-related quality of life (HRQoL), lower psychological well-being (PWB), and lower self-rated health. Very few studies have investigated the associations between use of various PHMs and QoL. One earlier study found a better quality of life among nursing home residents not receiving psychotropics than among those administered psychotropics (Galik and Resnick 2013). However, the adequate use of antidepressants seemed to positively affect quality of life (van de Ven-Vakhteeva et al. 2013). Use of DAPs has been associated with lower PWB (Teramura-Grönblad et al. 2011). In addition, high drug burden index (DBI) was associated with lower QoL (Bosboom et al. 2012), whereas use of Beers' drugs had no relationship with QoL (Franic and Jiang 2006, Bosboom et al. 2012). In any case, our findings suggest that the burden of PHMs is associated with lower HRQoL, although causality cannot be confirmed in this study.

No association was present between burden of PHMs at baseline and 3-year mortality. This is in line with most previous studies investigating the use of Beers' PIDs and mortality (Gupta et al. 1996, Onder et al. 2005, Klarin et al. 2005, Raivio et al. 2006, Pasina et al. 2014), although some studies have found an association (Lau et al. 2005, Perri et al. 2005). Results considering the use of DAPs and mortality have also been contradictory. According to a Finnish retrospective study among hip fracture patients, the use of DAPs was associated with mortality (Panula et al. 2009).

Other Finnish studies have observed no association between DAP use and increased mortality (Kumpula et al. 2011, Uusvaara et al. 2011). Gnjidic and colleagues in a population cohort study found a dose-response relationship between cumulative anticholinergic and sedative use and mortality (Gnjidic et al. 2014). Some other international studies have reported an association between DAPs and mortality (Fox et al. 2011, Lowry et al. 2011, Myint et al. 2015, Ruxton et al. 2015), while others have not found this association (Agar et al. 2010, Wilson et al. 2012, Dauphinot et al. 2014). Use of psychotropic drugs, especially antipsychotics, among people with dementia has been associated more clearly with mortality (Hartikainen et al. 2005, Schneider et al. 2005, Wang et al. 2005, Gill et al. 2007, Liperoti et al. 2009, Aparasu et al. 2012, Liperoti et al. 2017), although contradictory findings have also emerged for psychotropics (Raivio et al. 2007, Bell et al. 2009). The reason that the burden of PHMs was not reflected in a poor prognosis, i.e. mortality, in our study is probably due to the characteristics of the participants. They were very frail with a high number of serious comorbidities. Their prognosis was poor in any case, and improving their prognosis was challenging. Whether the medication of participants changed after the study period remains unknown.

6.5 Educational intervention to reduce the use of PHMs (Studies 2-4)

The intervention was educational and based on constructive learning theory and activating learning methods (Dolmans et al. 2005). This theory-based training may change the attitudes of nurses towards their patients. Training was based on nurses' own cases, which they had to elaborate. Most nurses participated willingly in training sessions and they were very interested and enthusiastic about education. There were many questions when discussing problems in their patients' medications and trying to find solutions. Trainers received favourable feedback from the nurses. Nurses were encouraged to discuss theirpatients' medication problems and to bring issues to their treating physicians, who were ultimately responsible for the medication. This kind of education may bring meaningfulness to nurses' work. Nurses are fairly independent in their work and carry much responsibility for their residents' medication. Treating physicians visit only once a week or even more rarely in assisted living facilities. In case of complications with a resident, nurses must contact their physicians or the doctor on call, and the decision about possible drug changes largely depends on how the nurse describes the situation. It is crucial that nursing staff have a wide knowledge about the actions and possible adverse effects of medications.

There was also some contradictory feedback; some nurses thought that this training was not suitable for nurses and that it only imposed upon their everyday work. There was some resistance to training. The reason for this remained unclear. One explanation may be that it is demanding to work in assisted living facilities, where residents are frail and physically disadvantaged. Most of them suffer from dementia and they may have behavioural symptoms, which is why the work is also psychologically challenging. Nurses may thus have been stressed, leading to the negative attitudes.

In this RCT, the intervention was designed to be quite light, lasting only two afternoons, and it was successful in decreasing the use of PHMs in the intervention group. This kind of intervention could easily be implemented in other units.

The use of PHMs, especially psychotropics, decreased in the intervention group compared with the control group. This finding is in line with previous educational intervention trials (Avorn et al. 1992, Meador et al. 1997, Schmidt et al. 1998a, Roberts et al. 2001, Fossey et al. 2006, Westbury et al. 2010, García-Gollarte et al. 2014). In addition to the modern learning methods used in this intervention, one explanation for the successful intervention effects might be the high use of PHMs at baseline.

HRQoL decreased significantly in both groups, but more slowly in the intervention group than in the control group. In this patient group, a large proportion suffered from dementia and other serious chronic diseases, inevitably leading to a decline in HRQoL. Thus, it is beneficial for the patient group even if the current HRQoL can be maintained or its decline slowed down. To our knowledge, this is the first educational PHM intervention to succeed with respect to HRQoL.

There was a lower number of hospital days in the intervention group than in the control group. This may be due to the decrease in complications related to adverse events of PHMs. The lower number of falls in the intervention group supports this speculation. However, the causal relationships between PHMs and hospitalizations cannot be confirmed in this study. To our knowledge, there is only one recent study in which use of health care services was reduced along with the reduction of PHMs (García-Gollarte et al. 2014).

There was a significant decrease in the number of falls per person per year in the intervention group compared with the controls. This is in line with two recent pharmacist-led studies to reduce PHMs (Patterson et al. 2010, Frankenthal et al. 2014). However, most earlier studies have not been able to show a reduction in falls along with the decrease in PHMs (Crotty et al. 2004, Fossey et al. 2006, García-Gollarte et al. 2014). The decrease in the number of falls in our study may be considered the

result of the educational intervention. The use of psychotropics decreased significantly in the intervention group, and some psychotropics represent a strong risk factor for falls (Hartikainen et al. 2007, Huang et al. 2012). It is necessary to restrict the excessive or inappropriate use of these drugs (Hill and Wee 2012, Huang et al. 2012).

Falls are common among older people, both home-dwelling and institutionalized (AGS and BGS 2011, Ambrose and Hausdorff 2013). Injuries and fractures may be the result of falls, and these may lead to hospitalization or utilization of other health services as well as to functional decline (AGS and BGS 2011). There are numerous risks for falling, both intrinsic (person-specific) and extrinsic (environmental) (Ambrose and Hausdorff 2013), and certain medications increase the risk for falling (Leipzig et al. 1999, Hartikainen et al. 2007, Huang et al. 2012). In addition to psychotropic drugs, several other drugs, such as some antihypertensives (increasing) and vitamin D (decreasing), may affect the risk for falling (Leipzig et al. 1999, Hien et al. 2005, Hartikainen et al. 2007, AGS and BGS 2011, Huang et al. 2012). At baseline, the intervention and control groups were similar in their use of these drugs. Those individuals with MMSE >10 seemed to benefit from the intervention with respect to falls, whereas those with <10 points did not. This may be due to the fact that those with severe dementia did not walk much any more, thus being at lower risk of falling than those with MMSE >10.

There was no effect on cognition in the intervention group relative to the control group. The effect of intervention was measured with clock drawing test and verbal fluency. Verbal fluency seemed to decrease in both groups, albeit not significantly. DAPs and some antipsychotics are known to negatively influence cognition (Schneider et al. 2006, Boustani et al. 2008, Rudolph et al. 2008, Campbell et al. 2009, Cancelli et al. 2009, Uusvaara et al. 2009). The use of DAPs did not decrease significantly in the intervention group relative to the control group. Therefore, it is logical that no difference was seen in cognition between the groups. The use of psychotropics decreased in the intervention group compared with the control group. However, the negative effect of psychotropics on cognition may be long-lasting. In a Finnish cohort study with a 6-month follow-up among residents aged ≥55 years, withdrawal of benzodiazepines as a hypnotic did not improve results in cognitive tests. Long-term daily users had slower reaction times at baseline and after the 6-month withdrawal than benzodiazepine-free controls (Puustinen et al. 2014).

In this study, participants were old (mean age 83-84 years), and 93% suffered from various degrees of dementia, with a mean MMSE ranging from 8.8 to 10. Thus, it was likely that the cognitive abilities of the participants will in any case slowly decrease.

Mortality was studied over the one-year follow-up of the RCT. There was no significant difference between the intervention and the control group in the multivariate model adjusted for age, sex, and comorbidities. In this RCT, the use of psychotropic drugs decreased significantly in the intervention group. Positive outcomes did not decrease the risk of participants' mortality, however, neither did the risk increase. Thus, the intervention was safe. Participants were old and had numerous serious comorbidities. MMSE scores were low, with mean values at 10. Thus, the participants had a high number of competing causes for death. According to a recent Cochrane review about interventions to improve prescribing for older people in care homes, there was no evidence of an effect of the intervention on mortality (Alldred et al. 2016). Our study is in line with this finding.

There were many favourable findings in this study: less harmful medications, especially psychotropics, fewer hospital days, fewer falls, and better QoL. However, we do not know how lasting these results will be. Staff turnover is frequent, requiring continuity in drug training. A large number of older people living in institutional settings suffer from dementia. Dementia is often associated with behavioural symptoms. These residents are treated with antipsychotic drugs even though their efficacy is limited (Sink et al. 2005). However, sometimes the residents need to be treated with antipsychotics, e.g. patients with psychotic symptoms. Anyway, the need for these medications should be evaluated regularly. In addition, nonpharmacological interventions are available to treat behavioural symptoms. Our study suggests that it is possible to decrease the use of harmful medications with a fairly light intervention.

7 Conclusions

1. The use of PHMs according to three different criteria (Beers' PIDs, DAPs, and concomitant use of >2 psychotropics) is highly prevalent among institutionalized older people (Study 1).
2. At baseline, the burden of potentially harmful medications (PHMs) was associated with a lower quality of life according to three different indicators: 15D HRQoL, PWB, and self-rated health. The burden of PHMs was not associated with mortality of participants (Study 1).
3. This kind of light intervention with two afternoon sessions is easy to implement in residential care units (Study 2).
4. RCT with educational intervention decreased the use of PHMs, especially psychotropic drugs (Study 3).
5. As a result of the educational intervention, HRQoL declined more slowly and the use of hospital days was lower in the intervention group than in the control group. No difference was present in mortality (Study 3).
6. As a result of the educational intervention, there were less falls in the intervention group than in the control group. No difference was present in changes of cognition (Study 4).

The use of PHMs is common among institutionalized older people. Their use can be reduced with an intervention that is easily implemented.

8 Implications for clinical practice and for future research

It is important to regularly assess the frail older patients' medications, which in an institutional setting include a high number of PHMs. The PHMs decrease QoL and increase risk of falling and hospitalizations. By decreasing the number of PHMs, especially psychotropics, clinicians can improve HRQoL and reduce falls and hospital days in this frail population.

Nurses are key persons to manage medications of residents in institutional settings. Activating training targeted to nurses is beneficial for the residents. This kind of educational intervention is light and easily implemented in institutional settings. It could also be part of nurses' continuing education. Staff turnover is high so it is important to regularly organize the training. Education on medication for older persons should be available also for consulting physicians and medical students.

Older people's medications frequently change. It is therefore important to assess and continually update the list of PHMs for the elderly. Computerized database systems should be constantly developed to recognize potential adverse drug reactions on the basis of drug lists in medical records.

The changes in PHMs over time should be explored in different institutional cohorts. Relevant outcomes for older people, such as QoL, falls, and use of health services, should be assessed simultaneously in these studies.

The present educational RCT should be repeated in different settings and cultures to determine whether the results can be generalized.

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11 Appendices

Appendix 1.
Comparison of Beers' 2003 and 2012 lists of inappropriate medications independent of diagnoses or conditions. Differences are highlighted. Changes in Beers' list 2015 (AGS 2015) are presented as footnotes in the table.

Beers 2003 (Fick et al. 2003)	Beers 2012 (AGS 2012)	Concerns /Comments
Anticholinergic drugs		
First-generation antihistamines:		Highly anticholinergic; tolerance when used as hypnotic; risk of confusion, dry mouth, constipation. Diphenhydramine can be used in certain situations like acute severe allergic reaction
	Brompheniramine	
	Carbinoxamine	
Chlorpheniramine	Chlorpheniramine	
	Clemastine	
Cyproheptadine	Cyproheptadine	
	Dexbrompheniramine	
Dexchlorpheniramine	Dexchlorpheniramine	
Diphenhydramine	Diphenhydramine (oral)	
	Doxylamine	
Hydroxyzine	Hydroxyzine	
Promethatzine	Prometahazine	
	Tripolidine	
Tripelennamine	Dropped 2012	
	Antiparkinson agents:	More effective alternatives available, not recommended for extrapyramidal (EP) symptoms caused by antipsychotics
	Benztropine (oral)	
	Trihexyphenidyl	
Gastrointestinal antispasmodic drugs:		Highly anticholinergic, effectiveness uncertain
Belladonna alkaloids	Belladonna-alkaloids	
Clidinium-chlordiazepoxide	Clidinium-chlordiazepoxide	
Dicyclomine	Dicyclomine	
Hyoscyamine	Hyoscyamine	
Propantheline	Propantheline	
	Scopolamine	
Muscle relaxants and antispasmodics:		Anticholinergic adverse effects, sedation, effectiveness uncertain
Carisoprodol	Carisoprodol	
Chlorzoxazone	Chlorzoxazone	
Cyclobenzaprine	Cyclobenzaprine	
Metaxalone	Metaxalone	
Methocarbamol	Methocarbamol	
Orphenadrine	Orphenadrine	
Oxybutynin (not extended-release)	Inappropriate with chronic constipation	Anticholinergic
Central nervous system drugs		
Tertiary tricyclic antidepressants, alone or in combination:		Strongly anticholinergic, sedating, may cause orthostatic hypotension. Compared with Beers' 2003, doxepin now has a maximum dose
Amitriptyline	Amitriptyline	
Chlordiazepoxide-amitriptyline	Chlordiazepoxide-amitriptyline	
	Clomipramine	
Doxepin	Doxepin >6 mg/d	
	Imipramine	
Perphenazine-amitriptyline	Perphenazine-amitriptyline	
	Trimipramine	
Daily fluoxetine	Dropped 2012	Long half-life, risk of CNS stimulation and agitation
Antipsychotics		Increased risk of stroke and death among persons with dementia
Conventional antipsychotics:		
	Chlorpromazine	
	Fluphenazine	

	Haloperidol	
	Loxapine	
	Molindone	
	Perphenazine	
	Pimozide	
	Promazine	
	Thiothixene	
	Trifluoperazine	
	Triflupromazine	
Mesoridazine	Mesoridazine	Anticholinergic, risk of QT-interval prolongation, EP adverse effects [1]
Thioridazine	Thioridazine	
Atypical antipsychotics:		
	Aripiprazole	
	Asenapine	
	Clozapine	
	Iloperidone	
	Lurasidone	
	Olanzapine	
	Paliperidone	
	Quetiapine	
	Risperidone	
	Ziprasidone	
Barbiturates:		High risk of physical dependence, tolerance when used for insomnia, risk of overdose at lowdosages
All barbiturates (except phenobarbital)		
	Amobarbital	
	Butabarbital	
	Butalbital	
	Mephobarbital	
	Pentobarbital	
	Phenobarbital	
	Secobarbital	
Benzodiazepines		
Doses of short- and intermediate-acting benzodiazepines:		Compared with Beers' 2003, there is no longer a maximum dose for benzodiazepines. They should be generally avoided among older people because they increase the risk of cognitive impairment, delirium, falls, and fractures. They may be appropriate in certain situations like ethanol or benzodiazepine withdrawal, rapid eye movement sleep disorders, and end-of-life care
Alprazolam >2 mg/d	Alprazolam	
	Estazolam	
Lorazepam >3 mg/d	Lorazepam	
Oxazepam >60 mg/d	Oxazepam	
Temazepam >15 mg/d	Temazepam	
Triazolam >0.25 mg/d	Triazolam	
Long-acting benzodiazepines and other sedatives:		
Chlorazepate	Chlorazepate	
Chlordiazepoxide	Chlordiazepoxide	
Chlordiazepoxide-amitriptyline	Chlordiazepoxide-amitriptyline	
Clidinium-chlordiazepoxide	Clidinium-chlordiazepoxide	
	Clonazepam	
Diazepam	Diazepam	
Flurazepam	Flurazepam	
Quazepam	Quazepam	
Halazepam	Dropped 2012	No longer available in USA
	Chloral hydrate	Tolerance, risk of overdose [2]
Meprobamate	Meprobamate	Very sedating and addictive
	Non-benzodiazepine hypnotics:	Adverse effects similar to those of benzodiazepines, avoid use of >90 days [3]
	Eszopiclone	
	Zolpidem	
	Zaleplon	
Other central nervous drugs		
Ergot mesyloids	Ergot mesylates	Ineffective
Cyclandelate	Dropped 2012	Ineffective

Isoxsuprine	Isoxsuprine	Ineffective
Amphetamines and anorexic agents	Dropped 2012	Risk of dependence, hypertension, angina pectoris, myocardial infarction; inappropriate in 2012 with insomnia
Pain		
Meperidine	Meperidine	Ineffective, may cause neurotoxicitylike confusion
Long-term use of NSAIDs:		Non-COX-selective NSAIDs, oral in Beers' 2012; risk of GI bleeding and peptic ulcer especially in those aged >75 years or taking corticosteroids, anticoagulants, or antiplatelet agents
	Aspirin > 325 mg/d	
	Diclofenac	
	Diflunisal	
	Etodolac	
	Fenoprofen	
	Ibuprofen	
	Ketoprofen	
	Meclofenamate	
	Mefenamic acid	
	Meloxicam	
	Nabumetone	
Naproxen	Naproxen	
Oxaprozin	Oxaprozin	
Piroxicam	Piroxicam	
	Sulindac	
	Tolmetin	
Indomethacin	Indomethacin	Of all NSAIDs, indomethacin has the most adverse effects
Ketorolac	Ketorolac	Asymptomatic GI bleedings
Pentazocine	Pentazocine	CNS adverse effects like confusion, safer alternatives available
Propoxyphene and combinations	Dropped 2012	No longer available in USA
Cardiovascular, antiarrhythmic drugs (Class Ia, Ic, III), and antithrombotics		
Doxazosin	Doxazosin	Alpha agonists. May cause hypotension, dry mouth, and urinary problems
	Prazosin	
	Terazosin	
Clonidine	Clonidine	Alpha agonists, central. Orthostatic hypotension, CNS effects
	Guanabenz	
	Guanfacine	
Methyldopa, methyldopa-hydrochlortiazide	Methyldopa	Alpha agonists. Risk of bradycardia and depression
Reserpine at doses > 0.25 mg	Reserpine (>0.1 mg/d)	Alpha agonist. Depression, sedation, orthostatism
Amiodarone	Amiodarone	Risk of QT-interval prolongation and torsade de pointes tachycardia, pulmonary disorders, thyroid disorders
	Dofetilide	Rate control yields better balance than rhythm control, antiarrhythmic drugs should be avoided as first-line treatment of atrial fibrillation [4]
	Dronedarone	
	Flecainide	
	Ibutilide	
	Procainamide	
	Propafenone	
	Quinidine	
	Sotalol	
Disopyramide	Disopyramide	Strongly anticholinergic, risk of heart failure in elderly patients
Digoxin >0.125 mg/d	Digoxin > 0.125 mg/d	Risk of toxic effects for decreased renal clearance among older people
Short acting nifedipine	Nifedipine, immediate release	May cause hypotension and constipation

	Spironolactone > 25 mg/d	Hyperpotassaemia, especially if taking NSAID, ACE-inhibitor, AT-receptor blocker, or potassium supplement
Guanethidine Guanadrel	Dropped 2012	Risk of orthostatic hypotension
Ethacrynic acid	Dropped 2012	Risk of hypertension and fluid imbalance
Short-acting dipyridamole	Short-acting dipyridamole	Risk of orthostatic hypotension
Ticlopidine	Ticlopidine	No better than aspirin, more toxic
Gastrointestinal drugs and others		[5, 6]
Bisacodyl Cascara sagrada	Dropped 2012	Risk of bowel dysfunction Long-term use of stimulant laxatives, except when using opiates
Mineral oil	Mineral oil	Risk of aspiration
Trimethobenzamide	Trimethobenzamide	Extrapyramidal adverse effects [7]
	Metoclopramide	Risk of extrapyramidal side effects, even tardive dyskinesia
Cimetidine	Dropped 2012	CNS adverse effects, confusion; 2012 inappropriate with delirium
Nitrofurantoin	Nitrofurantoin	Risk of pulmonary toxicity, ineffective when GFR <60 ml/min [8]
Ferrous sulphate >325 mg/d		Risk of constipation, absorption is no better with higher doses
Drugs for endocrine disorders		
Oestrogens only (oral)	Oestrogens with or without progestins	Risk of breast and endometrium cancer, vaginal oestrogens for treatment of vaginal dryness seem to be safe when oestradiol < 25 µg twice a week
Methyltestosterone	Methyltestosterone	Risk of prostatic hypertrophy, cardiac problems, contraindicated in men with prostatic cancer
	Testosterone	
Desiccated thyroid	Desiccated thyroid	May cause cardiac effects
	Growth hormone	Risk of oedema, arthralgia, gynaecomastia, allowed only if pituitary gland removed
	Insulin, sliding scale	Risk of hypoglycaemia[9]
	Megestrol	Risk of thrombotic events and possibly death
Chlorpropamide	Chlorpropamide	Risk of prolonged hypoglycaemia and SIADH
	Glyburide	Risk of prolonged hypoglycaemia

[1] Mesoridazine removed, no longer marketed in USA, [2] Chlorarl hydrate removed, no longer marketed in USA [3] Non-benzodiazepine hypnotics are always to be avoided, [4] Antiarrhythmic drugs except disopyramide, and dronedarone removed and amiodarone and digoxin as first-line treatment for atrial fibrillation, [5] PPIs added, should be evaluated after 8 weeks of use, risk of *Clostridium difficile* infection and bone fractures, [6] Desmopressin added to genitourinary drugs, risk of hyponatremia, [7] Trimethobenzamide removed,[8] Nitrofurantoin can be used short time carefully in individual with GFR ≥30 ml/min, [9] Insulin, sliding scale - rationale modified, ACE=angiotensin converting enzyme, AT=angiotensin, CNS=central nervous system, COX=cyclo-oxygenase, EP=extrapyramidal, GFR=glomerular filtration rate, GI=gastrointestinal, NSAID=non-steroidal anti-inflammatory drugs

Appendix 2.

Beers' inappropriate drugs 2003 available in Finland 2011-2012.

Drug	ATC-CODE	Concern
Indomethacin	M01AB01	Produces the most CNS adverse effects of all available non-steroidal anti-inflammatory drugs
Oxybutynin	G04BD04	Causes anticholinergic adverse effects and effectiveness is questionable
Amitriptyline	N06AA09	Amitriptyline and doxepin are strong anticholinergic and sedating, not good choices for older people, chlordiazepoxide is a long-acting benzodiazepine
Amitriptyline- chlordiazepoxide	N06CA01	
Amitriptyline-perphenazine	N06CA01	
Doxepin	N06AA12	
Meprobamate	N05BC01	Highly addictive and sedating
Lorazepam >3 mg/day	N05BA06	Older people are very sensitive to benzodiazepines, smaller doses may be as effective and safer
Oxazepam >60 mg/day	N05BA04	
Alprazolam >2 mg/day	N05BA12	
Temazepam >15 mg/day	N05CD07	
Triazolam >0.25 mg/day	N05CD05	
Chlordiazepoxide	N05BA02	Have a long half-life in older people, producing prolonged sedation and the risk for falls and fractures
Chlordiazepoxide-clidinium	A03CA02	
Diazepam	N05BA01	
Digoxin >0.12 5mg/day	C01AA05	Older people' decreased renal clearance may lead to increased risk of toxic effects
Dipyridamole (short-acting)	B01AC07	Risk for orthostatic hypotension
Belladonna-alkaloids	A03BB	Highly anticholinergic and effectiveness is uncertain
Diphenhydramine	D04AA32	Highly anticholinergic
Hydoxyzine	N05BB01	
Ergot mesyloids	C04AE01	Not effective in the doses studied
Ferrous sulphate >325 mg/day	B03A	Higher doses do not increase the absorption, but increase the incidence of constipation
Ketorolac	M01AB15	May cause a lot of asymptomatic GI pathologic conditions
Amphetamines (excluding methylphenidate hydrochloride and anorexics)	N06BA	CNS stimulant adverse effect
Naproxen	M01AE02	Risk for GI bleedings, renal failure, high blood pressure, and heart failure
Piroxicam *	M01AC01	
Fluoxetine	N06AB03	Long half-life, risk for CNS stimulation, sleep disturbances, and agitation
Bisacodyl, cascara sagrada, and Neoloid **	A06AB02	Risk for bowel dysfunction
Amiodarone	C01BD01	Risk for QT-interval prolongation and torsades de pointes arrhythmias
Orphenadrine	M03BC01	Anticholinergic adverse effects and sedation
Nitrofurantoin	J01XE01	Risk for renal impairment, safer alternative available
Nifedipine (short-acting)	C08CA05	Risk for hypotension and constipation
Clonidine	C02AC01	Risk for orthostatic hypotension and CNS adverse effects
Cimetidine	A02BA01	CNS adverse effects like confusion
Oestrogens only (oral)	G03C	Risk for breast and endometrial carcinoma, lack of cardioprotective effect in older women

* In Finland, only topically available, not considered inappropriate in study

**If used twice a week = regular use. Not considered inappropriate in study if opioid in use

Appendix 3.

Drugs with anticholinergic property.

Drug	ATC-CODE	Rudolph et al. 2008	Socialstyrelsen 2010	Fick et al. 2003	Included[1]
Alimemazine	R06AD01		+		
Amantadine	N04BB01	+			
Amitriptyline	N06AA09	+	+	+	X
Atropine	A03BA01	+	+		
Baclofen	M03BX01	+			X
Belladonna alkaloids	A03BA04			+	
Benztropine	N04AC01	+			
Biperidene	N04AA02		+		X
Butylscopolamine	A03BB01		+		
Carbidopa-levodopa	N04BA01	+			X
Carisoprodol	M03BA02	+		+	
Cetrizine	R06AE07	+			X
Chlorpheniramine	R06AB02	+	+	+	
Chlorpromazine	N05AA01	+			X
Chlorprotixene	N05AF03		+		X
Chlorzoxazone	M03BB03			+	
Cimetidine	A02BA51	+			
Clidinium bromide	A03CA02				
Clinidine-chlordiazepoxide	N05BA02			+	X
Clomipramine	N06AA04		+		X
Clozapine	N05AH02	+	+		X
Codeine	R05DA04				
Cyclobenzaprine	M03BX08	+	+	+	
Cyproheptadine	R06AX02	+	+	+	
Dariphenasine	G04BD		+		X
Desipramine	N06AA01	+			
Dexchlorpheniramine	R06AB52		+	+	
Dicyclomine	A03AA07	+		+	
Dimenhydrinate	R06AA52		+		
Diphenhydramine	R06AA02	+		+	X
Dipyridamole	B01AC07			+	X
Disopyramide	C01BA03		+	+	
Doxepin	N06AA12			+	X
Entacapone	N04BX02	+			X
Fesoterodine	G04BD		+		X
Fluphenazine	N05AB02	+			X
Glycopyrrone	R03BB06		+		X
Haloperidol	N05AD01	+			X
Hydroxyzine	N05BB01	+	+	+	X
Hyoscyamine	A03BA03	+	+	+	
Imipramine	N06AA02	+			
Levomepromazine	N05AA02		+		X
Loperamide	A07DA03	+			X
Loratadine	R06AX13	+			X
Maprotiline	N06AA21		+		
Meclizine	R06AE05	+			
Methocarbamol	M03BA03	+		+	
Methylscopolamine	A03BB03		+		
Metoclopramide	A03FA01	+			X
Mirtazapine	N06AX11	+			X
Morphine	N02AG		+		

Nortriptyline	N06AA10	+	+		X
Olanzapine	N05AH03	+			X
Orphenadrine	M03BC01			+	X
Oxybutynin	G04BD04	+	+	+	X
Paroxetine	N06AB05	+			X
Perphenazine	N05AB03	+		+	X
Pramipexole	N04BC05	+			X
Prochlorperazine	N05AB04	+			X
Promethazine	D04AA10	+	+	+	
Propantheline	A03AB05			+	
Pseudoephedrine	R01BA02	+			X
Quetiapine	N05AH04	+			X
Ranitidine	A02BA02	+			X
Risperidone	N05AX08	+			X
Scopolamine	A04AD01		+		X
Selegiline	N04BD01	+			X
Soliphenasine	G04BD		+		X
Thiethylperazine	R06AD03		+		
Thioridazine	N05AC02	+			
Thiothixene	N05AF04	+			
Tizanidine	M03BX02	+			X
Tolterodine	G04BD	+	+		X
Trazodone	N06AX05	+			X
Trifluoperazine	N05AB06	+			
Trihexyphenidyl	N04AA01		+		
Tripelennamine	R06AC04			+	
Ziprasidone	N05AE04	+			X

[1]Included anticholinergic drugs in this study

Appendix 4.

Psychotropic and other drugs considered potentially harmful medications (PHMs) in addition to Beers 2003 and DAPs.

ATC-group	Drug	ATC-code
N05A Antipsychotics	Chlorpromazine	N05AA01
	Levomepromazine	N05AA02
	Fluphenazine	N05AB02
	Perphenazine	N05AB03
	Periciazine	N05AC01
	Haloperidol	N05AD01
	Droperidol	N05AD08
	Sertindole	N05AE03
	Ziprasidone	N05AE04
	Flupentixol	N05AF01
	Chlorprothixene	N05AF03
	Zuclopenthixol	N05AF05
	Loxapine	N05AH01
	Clozapine	N05AH02
	Olanzapine	N05AH03
	Quetiapine	N05AH04
	Asenapine	N05AH05
	Sulpride	N05AL01
	Lithium	N05AN01
	Risperidone	N05AX08
	Aripiprazole	N05AX12
	Paliperidone	N05AX13
N06A Antidepressants	Clomipramine	N06AA04
	Trimipramine	N06AA06
	Amitriptyline	N06AA09
	Nortriptyline	N06AA10
	Doxepin	N06AA12
	Fluoxetine	N06AB03
	Citalopram	N06AB04
	Paroxetine	N06AB05
	Sertraline	N06AB06
	Fluvoxamine	N06AB08
	Escitalopram	N06AB10
	Moclobemide	N06AG02
	Mianserin	N06AX03
	Trazodone	N06AX05
	Mirtazapine	N06AX11
	Bupropion	N06AX12
	Venlafaxine	N06AX16
	Reboxetine	N06AX18
	Duloxetine	N06AX21
	Agomelatine	N06AX22
	Hyperici herba	N06AX25
N05B Anxiolytics	Diazepam	N05BA01
	Chlordiazepoxide	N05BA02
	Oxazepam	N05BA04
	Lorazepam	N05BA06
	Clobazam	N05BA09
	Alprazolam	N05BA12
	Hydroxyzine	N05BB01
	Buspirone	N05BE01
N05C Hypnotics	Nitrazepam	N05CD02
	Triazolam	N05CD05
	Temazepam	N05CD07
	Midazolam	N05CD08
	Zopiclone	N05CF01

	Zolpidem	N05CF02
	Zaleplon	N05CF03
	Melatonin	N05CH01
	Valerianae radix	N05CM09
	Dexmedetomidine	N05CM18
A02BC Proton pump inhibitors	Omeprazole	A02BC01
	Pantoprazole	A02BC02
	Lansoprazole	A02BC03
	Rabeprazole	A02BC04
	Esomeprazole	A02BC05
M01A Non-steroidal anti-inflammatory drugs	Indometacin	M01AB01
	Diclofenac	M01AB05
	Etodolac	M01AB08
	Ketorolac	M01AB15
	Meloxicam	M01AC06
	Ibuprofen	M01AE01
	Naproxen	M01AE02
	Ketoprofen	M01AE03
	Dexketoprofen	M01AE17
	Mefenamic acid	M01AG01
	Tolfenamic acid	M01AG02
	Celecoxib	M01AH01
	Parecoxib	M01AH04
	Etoricoxib	M01AH05

Appendix 5. Mini Nutritional Assessment (MNA) (Guigoz et al. 2002).

Ravitsemustilan arviointi MNA

Nimi_____ Sukupuoli_____ Ikä_____

Pituus (cm)_____ Paino (kg)_____ Päivämäärä_____

Merkitse pisteet ruutuihin ja laske yhteen. Jos seulonnan kokonaispistemäärä on 11 tai vähemmän, jatka loppuun asti.

Seulonta

A. Onko ravinnonsaanti vähentynyt viimeisen kolmen kuukauden aikana ruokahaluttomuuden, ruuansulatusongelmien, puremis- tai nielemisvaikeuksien takia

0 = Kyllä, ravinnonsaanti on vähentynyt huomattavasti
1 = Kyllä, ravinnonsaanti on vähentynyt hieman
2 = Ei muutoksia ☐

B. Painonpudotus kolmen viime kuukauden aikana

0 = painonpudotus yli 3 kg
1 = ei tiedä
2 = painonpudotus 1-3 kg
3 = ei painonpudotusta ☐

C. Liikkuminen

0 = vuode- tai pyörätuolipotilas
1 = pääsee ylös sängystä, mutta ei käy ulkona
2 = liikkuu ulkona ☐

D. Onko viimeisen kolmen kuukauden aikana ollut psyykkistä stressiä tai akuutti sairaus

0 = kyllä 2 = ei ☐

E. Neuropsykologiset ongelmat

0 = dementia, depressio tai neuropsykologinen ongelma
1 = lievä dementia, depressio tai neuropsykologinen ongelma
2 = ei ongelmia ☐

F. Painoindeksi eli BMI (= paino / (pituus)^2 kg/m^2)

0 = BMI on alle 19
1 = BMI on 19 tai yli mutta alle 21
2 = BMI on 21 tai yli mutta alle 23
3 = BMI on 23 tai enemmän ☐

Seulonnan tulos (maksimi 14 pistettä) ☐☐
12 pistettä tai enemmän -> riski virheravitsemukselle ei ole kasvanut, arviointia ei tarvitse jatkaa
11 pistettä tai vähemmän -> riski virheravitsemukselle on kasvanut, jatka arviointia

Arviointi

G. Asuuko haastateltava kotona

0 = ei 1 = kyllä ☐

H. Onko päivittäisessä käytössä useampi kuin kolme reseptilääke

0 = kyllä 1 = ei ☐

I. Painehaavaumia tai muita haavoja iholla

0 = kyllä 1 = ei ☐

J. Päivittäiset lämpimät ateriat (sisältää puurot ja vellit)

0 = 1 ateria
1 = 2 ateriaa
2 = 3 ateriaa ☐

K. Sisältääkö ruokavalio vähintään kyllä ei

- yhden annoksen maitovalmisteita (maito, juusto, piimä, viili) päivässä ☐ ☐
- kaksi annosta tai enemmän kananmunia viikossa (myös ruuissa, esim. laatikot) ☐ ☐
- lihaa, kalaa tai linnun lihaa joka päivä ☐ ☐

0 = jos 0 tai 1 kyllä-vastausta
0,5 = jos 2 kyllä-vastausta
1 = jos 3 kyllä-vastausta ☐

L. Kuuluuko päivittäiseen ruokavalioon kaksi tai useampia annoksia hedelmiä tai kasviksia

0 = ei 1 = kyllä ☐

M. Päivittäinen nesteen juonti (esim. kahvi, tee, maito, mehu, kotikalja tai vesi)

0 = alle 3 lasillista
0,5 = 3 - 5 lasillista
1 = enemmän kuin 5 lasillista ☐

N. Ruokailu

0 = tarvitsee paljon apua tai on syötettävä
1 = syö itse, mutta tarvitsee hieman apua
2 = syö itse ongelmitta ☐

O. Oma näkemys ravitsemustilasta

0 = vaikea virhe- tai aliravitsemus
1 = ei tiedä tai lievä virhe- tai aliravitsemus
2 = ei ravitsemuksellisia ongelmia ☐

P. Oma näkemys terveydentilasta verrattuna muihin samanikäisiin

0 = ei yhtä hyvä
0,5 = ei tiedä
1 = yhtä hyvä
2 = parempi ☐

Q. Olkavarren keskikohdan ympärysmitta (OVY cm)

0 = OVY on alle 21 cm
0,5 = OVY on 21-22 cm
1,0 = OVY on yli 22 ☐

R. Pohkeen ympärysmitta (PYM cm)

0 = PYM on alle 31 cm
1 = PYM on 31 cm tai enemmän ☐

Arviointi (maksimi 16 pistettä) ☐☐
Seulonta (maksimi 14 pistettä) ☐☐
Kokonaispistemäärä (maksimi 30 pistettä) ☐☐

Asteikko:
1. yli 23,5 pistettä: hyvä ravitsemustila ☐
2. 17-23,5 pistettä: riski virheravitsemukselle kasvanut ☐
3. alle 17 pistettä: kärsii virhe- tai aliravitsemuksesta ☐

Appendix 6. Mini-Mental State Examination (MMSE) (Folstein et al. 1975).

MINI-MENTAL STATE EXAMINATION

POTILAS: _____ SYNTYMÄAIKA:_____

TUTKIJA: _____PVM:_____

Seuraavassa esitän Teille erilaisia pieniä muistiin ja älyllisiin toimintoihin liittyviä kysymyksiä ja tehtäviä:

		Väärin	Oikein
1.	**Mikä vuosi nyt on?**	0	1
2.	**Mikä vuodenaika nyt on?**	0	1
	(talvi = joulu, tammi, helmi kevät = maalis, huhti, touko kesä = kesä, heinä, elo syksy = syys, loka, marras; aina ± 1 vko)		
3.	**Monesko päivä tänään on? (± 1 pv)**	0	1
4.	**Mikä viikonpäivä tänään on?**	0	1
5.	**Mikä kuukausi nyt on?**	0	1
6.	**Missä maassa olemme?**	0	1
7.	**Missä maakunnassa olemme?** (Myös vanhan läänijaon mukaiset vastaukset hyväksytään)	0	1
8.	**Mikä on tämän paikkakunnan nimi?**	0	1
9.	**Mikä on tämä paikka jossa olemme?** (Sairaalan/terveyskeskuksen nimi, kotiosoite)	0	1
10.	**Monennessako kerroksessa olemme?**	0	1
11.	**Seuraavassa pyydän Teitä painamaan mieleen kolme sanaa. Kun olen sanonut ne, toistakaa perässäni.** (Kaksi vaihtoehtoista sarjaa) **PAITA – RUSKEA – VILKAS** **RUUSU – PALLO – AVAIN** PAITA RUUSU 0 1 RUSKEA tai PALLO 0 1 VILKAS AVAIN 0 1 (Merkitään ensimmäisellä kerralla muistetut sanat. Jos ensimmäisessä toistossa tulee virheitä, sanoja kerrataan, kunnes kaikki kolme sanaa on opittu.) Toistoja____(enintään 5 kertaa).		
12.	**Nyt pyydän Teitä vähentämään 100:sta 7 ja saamastanne jäännöksestä 7 ja edelleen vähentämään 7, kunnes pyydän lopettamaan.** 93..... 0 1 86..... 0 1 79..... 0 1 72..... 0 1 65..... 0 1 (Kysymys voidaan toistaa kerran, jos sitä ei heti ymmärretä. Jos henkilö tekee välillä virheen, mutta jatkaa siitä oikein vähentäen 7 virheellisestä luvusta, tulee vääriä vastauksia 1. Kynää ja paperia ei saa käyttää.)		

		Väärin	Oikein
13.	**Mitkä olivat ne kolme sanaa, jotka pyysin Teitä painamaan mieleenne?** (Sanojen järjestyksellä ei ole merkitystä.) PAITA RUUSU 0 1 RUSKEA tai PALLO 0 1 VILKAS AVAIN 0 1		
14.	**Nyt kysyn Teiltä kahden esineen nimeä.** **a) Mikä tämä on?** – näytetään rannekelloa 0 1 **b) Mikä tämä on?** – näytetään lyijykynää 0 1		
15.	**Nyt luen Teille lauseen. Pyydän Teitä toistamaan sen perässäni:** **EI MITÄÄN MUTTIA EIKÄ JOSSITTELUA** 0 1 (Annetaan piste vain, jos lause on täysin oikein. Lausetta ei saa toistaa.)		
16.	**Seuraavaksi annan Teille paperin ja pyydän Teitä tekemään sille jotain.** (Paperi asetetaan pöydälle tutkittavan eteen.) **Ottakaa paperi vasempaan käteenne. Taittakaa se keskeltä kahtia ja asettakaa polvienne päälle.** (Ohjeita ja lausetta ei saa toistaa eikä henkilöä saa auttaa.) Ottaa paperin vasempaan käteen 0 1 Taittaa sen 0 1 Asettaa paperin polville 0 1		
17.	**Näytän Teille tekstin ”SULKEKAA SILMÄNNE”. Pyydän Teitä lukemaan sen ääneen ja noudattamaan sen ohjetta.** 0 1 (Annetaan piste vain, jos sekä lukee tekstin että sulkee silmänsä.)		
18.	**Kirjoittakaa kokonainen lyhyt lause mielenne mukaan.** (ks. seuraava sivu) 0 1 (Yksi piste, jos lause on ymmärrettävä ja siinä on ainakin subjekti ja predikaatti. Kirjoitusvirheet eivät vaikuta.)		
19.	**Voisitteko piirtää tämän kuvion alapuolelle samanlaisen kuvion.** (ks. seuraava sivu) 0 1 (Annetaan piste, jos kaikki sivut ja kulmat ovat tallella ja leikkauspinta on nelikulmainen.)		

MMSE-testin pistemäärä _____ /30

KÄÄNNÄ

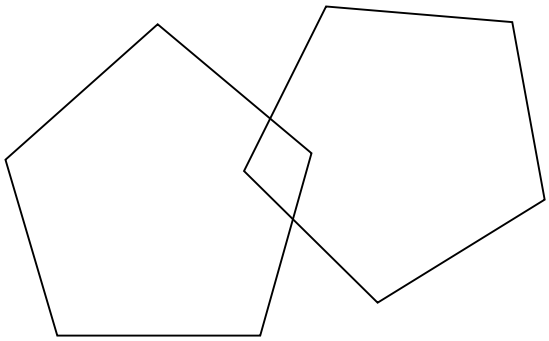
Kirjoittaisitteko lauseen tähän.

_____

_____

_____

Piirtäisittekö tämän kuvion alapuolelle samanlaisen kuvion.



SULKEKAA SILMÄNNE

Appendix 7. CDR, clock drawing test and verbal fluency

Taulukko 1. Kirjaa ruudukkoon haastattelun perusteella potilaan toimintakyky kullakin CDR-luokituksen osa-alueella.					
Osa-alue	**CDR 0, ei dementiaa**	**CDR 0.5, mahdollinen**	**CDR 1, lievä**	**CDR 2, keskivaikea**	**CDR 3, vaikea**
Muisti	Ei muistin huonontumista tai pientä muistamattomuutta toisinaan.	Lievää jatkuvaa muistamattomuutta; tapahtumien osittaista muistamista; "hyvänlaatuista" muistamattomuutta. *Esim."hajamielisyys", nimet unohtuvat*	Kohtalaista muistin huonontumista, selvempänä koskien viimeaikaisia tapahtumia; vaikuttaa jokapäiväisiin toimintoihin. *Esim. ei muista tapaamisia, edellisenä päivänä sovittuja asioita*	Vaikea muistihäiriö, vain hyvin opittu aines säilynyt; uusi aines unohtuu pian. *Esim. Kyselee samoja asioita uudelleen. Viime aikaiset tapahtumat hukassa.*	Vaikea muistihäiriö; vain pirstaleita säilynyt. *Esim. Ei muista elämänsä tapahtumia kuin pirstaleina*
Orientaatio	Täysin orientoitunut.	Täysin orientoitunut lukuun ottamatta pieniä vaikeuksia aikasuhteissa. *Esim. ei muista päivämäärää.*	Jonkin verran vaikeuksia aikasuhteissa; tutkimustilanteessa orientoitunut paikkaan; muuten voi olla maantieteellistä desorientaatiota. *Esim. vieraassa paikassa ei muista paikan nimeä tai vaikeus muistaa viikonpäivää*	Suuria vaikeuksia aikasuhteissa; yleensä desorientoitunut aikaan ja usein paikkaan. *Esim. saattaisi eksyä ulkona ilman saattajaa*	Orientoitunut vain henkilöön. *Tietää oman nimensä mutta tuttujenkin henkilöiden nimet unohtuvat, eksyy tutussakin ympäristössä*
Arvostelukyky	Ratkaisee jokapäiväiset ongelmat ja hoitaa taloudelliset asiansa hyvin; arvostelukyky hyvin säilynyt.	Vain vähäistä huonontumista ratkaistaessa ongelmia, yhtäläisyyksiä, eroja. *Esim. monimutkaiset ongelmanratkaisut tuottavat vaikeuksia (vaikeat laskutehtävät, päätöksenteko isojen raha-asioiden suhteen)*	Kohtalaisia vaikeuksia käsiteltäessä ongelmia, yhtäläisyyksiä ja eroja; sosiaalinen arvostelukyky yleensä säilynyt. *Esim. Ei pysty käyttämään euroja*	Merkittäviä vaikeuksia käsiteltäessä ongelmia, yhtäläisyyksiä ja eroja; sosiaalinen arvostelukyky yleensä heikentynyt. esim. *Ei pysty hoitamaan lainkaan esim. kauppa-asioita, lääkkeitään.*	Arvostelukyvytön ja kyvytön ratkaisemaan ongelmia.
Yhteisölliset toiminnot	Toimii itsenäisesti tavanomaisella tasollaan työelämässä, ostosten teossa sekä vapaaehtoistyössä ja sosiaalisissa ryhmissä.	Vain vähäistä huonontumista em. toiminnoissa.	Kyvytön toimimaan itsenäisesti em. toiminnoissa joskin saattaa silti olla mukana joissakin; voi edelleen vaikuttaa normaalilta satunnaisesta tarkkailijasta.	Ei itsenäistä toimintaa kodin ulkopuolella, joskin kykenee saatettuna osallistumaan kodin ulkopuoliseen toimintaan.	Ei itsenäistä toimintaa kodin ulkopuolella; ei saatettunakaan kykene osallistumaan tällaiseen toimintaan.
Koti ja harrastukset	Eläminen kotona, älyllinen mielenkiinto ja harrastukset hyvin säilyneet.	Eläminen kotona, älyllinen mielenkiinto ja harrastukset korkeintaan lievästi heikentyneet.	Lievää mutta selkeää huonontumista toiminnoissa kotona; luopunut vaikeammista askareista (*esim. ruoanlaitto)* ; luopunut monimutkaisemmista harrastuksista ja toiminnoista.	Vain yksinkertaisimmat askareet sujuvat; hyvin rajatut kiinnostuksen kohteet; huonosti keskittyvä. *Esim. pystyy vain yhdessä ohjattuna osallistumaan kotitöihin*	Ei merkittävää toimintaa kotona.
Itsestä huolehtiminen	Täysin kykenevä huolehtimaan itsestään.	Täysin kykenevä huolehtimaan itsestään.	Tarvitsee kehotuksia ja muistutuksia. *(peseytyminen, pukeutuminen, syöminen)*	Tarvitsee apua pukemisessa, henkilökohtaisessa hygieniassa ja henkilökohtaisten tavaroidensa hoidossa.	Tarvitsee paljon apua itsestään huolehtimisessa; usein pidätyskyvyttämyyttä.

Tutkittavan nimi _____ Nro _____
Pvämäärä _____

Kellotestin tulos _____ pistettä
Piirtäkää kellotaulu, jossa on numerot ja viisarit. Kello osoittaa 10 yli 11.

Verbal flow :

_____

_____

_____

_____

_____

_____

_____

_____

Yhteensä _____kpl eläimiä /min

Appendix 8. Psychological well-being (PWB) (Routasalo et al. 2009).

PÄIVÄMÄÄRÄ _____

POTILAAN NIMI _____ NRO _____

Seuraavaksi vielä muutama kysymys elämänasenteistanne

1. Oletteko tyytyväinen elämäänne? kyllä en

2. Tunnetteko itsenne tarpeelliseksi? kyllä en

3. Onko Teillä tulevaisuudensuunnitelmia? kyllä ei

4. Onko Teillä elämänhalua? kyllä ei

5. Oletteko masentunut?
   1. harvoin tai ei koskaan
   2. toisinaan
   3. usein tai aina

4. Kärsittekö yksinäisyydestä?
   1. harvoin tai ei koskaan
   2. toisinaan
   3. usein tai aina

5. **Millaiseksi arvioitte oman terveydentilanne tällä hetkellä (tutkittavalta)**

1 Pidän itseäni terveenä

2 Pidän itseäni melko terveenä

3 Pidän itseäni sairaana

4 Pidän itseäni hyvin sairaana

12 Original publications